Faecal incontinence and the role of percutaneous tibial nerve stimulation

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Statement of originality

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Chapter 4

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Publications and presentations

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The clinical effectiveness of neuromodulation in the treatment of faecal incontinence: a systematic review.

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Co-existing faecal incontinence and rectal evacuatory disorder following childbirth: an under-reported phenomenon

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Post-partum defecatory dysfunction: a complex problem involving co-existing faecal incontinence and constipation.

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Under-recognised co-existence of constipation and faecal incontinence in the adult population: a large single-centre experience.

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Quality of anal evoked potential (AEP) recordings is reduced in patients with faecal incontinence (FI): Evidence of central sensory pathway dysfunction?

Carrington EV, **Horrocks EJ**, Burgell R, Bjerke A, Connolly S, Scott SM, Jones JFX, O'Connell PR, Knowles CH.

Society of Academic and Research Surgery. Durham. January 2015.

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Abstract

Aims and objectives

This thesis aimed to assess the efficacy of percutaneous tibial nerve stimulation (PTNS) in the treatment of adults with faecal incontinence (FI). The objectives were (1) to perform a systematic review of the evidence base for tibial nerve stimulation (TNS) to treat FI, (2) to assess the short term efficacy of PTNS in the treatment of FI (the CONFIDeNT Trial), (3) to identify factors predictive of successful PTNS and (4) to analyse the 1-year outcomes of all patients in the CONFIDeNT Trial.

Methods

Objective 1: A systematic review of the current literature on TNS in the treatment of FI was performed. Objective 2: A multi-centre double blind randomised sham-controlled trial comparing PTNS to sham electrical stimulation in the treatment of adults with FI was performed. Objective 3: Logistic regression analysis to identify factors predictive of successful PTNS from the CONFIDeNT Study data was performed. Objective 4: A 1-year follow-up study of patients enrolled in The CONFIDeNT Study was performed.

Results

Data supporting the use of PTNS in the treatment of adults with FI was encouraging, however data quality was poor. In the short term, PTNS did not offer significant clinical benefit over sham electrical stimulation in the treatment of adults with FI, based on the primary outcome (treatment success was defined as ≥50% reduction in weekly FI episodes). Logistic regression analysis demonstrated the absence of any difficulty with rectal evacuation was the only factor predictive of successful PTNS in the short term (directly after treatment). The follow-up study demonstrated the continued benefit of treatment in the proportion of patients followed to 1-year.

Conclusions

PTNS should not be recommended as a first-line treatment for unselected adults with FI (the population in CONFIDeNT Trial). However, subgroups of patients, e.g. those with FI uncomplicated by problems with rectal evacuation, may benefit more. In patients gaining benefit, this appears to be sustained.

Contents

Figures

Tables

List of abbreviations

AAS	Artificial anal sphincter
CCIS	Cleveland Clinic Incontinence Score
CONFIDeNT	CONtrol of Faecal Incontinence using Distal NeuromodulaTion (project title)
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
DSMC	Data Safety and Monitoring Committee
EAUS	Endoanal ultrasound scanning
FDA	Food and Drug Administration
FI	Faecal incontinence
FIE	Faecal incontinence episodes
FIQOL	Faecal Incontinence Quality of Life Scale
GIQOL	Gastrointestinal Quality of Life Index
GN	Gracilis neosphincter
GRA	Global response assessment
ICC	Intracluster coefficient
IQR	Interquartile range
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OAB	Overactive bladder
OASIS	Obstetric anal sphincter injuries
ODS	Obstructed Defaecation Score
PCTU	Pragmatic Clinical Trials Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTNS	Percutaneous tibial nerve stimulation
QOL	Quality of life

RAIR	Rectoanal inhibitory reflex
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SF-36	Short form-36 questionnaire
SMCS	St Mark's Continence Score
TENS	Transcutaneous electrical nerve stimulation
TMG	Trial Monitoring Group
TNS	Tibial nerve stimulation
TSC	Trial Steering Committee
TTNS	Transcutaneous tibial nerve stimulation
VAS	Visual analogue scale

1 Introduction

1.1 Definitions

Faecal incontinence (FI) is described as the 'recurrent uncontrolled passage of faecal material, for at least three months'[1]. The loss of wind (flatus) can also be a problem, and this, in addition to FI as described above, is often called anal incontinence[2-4]. FI occurs when one or more of the mechanisms that maintain continence is disrupted, and the other mechanisms are unable to fully compensate[5].

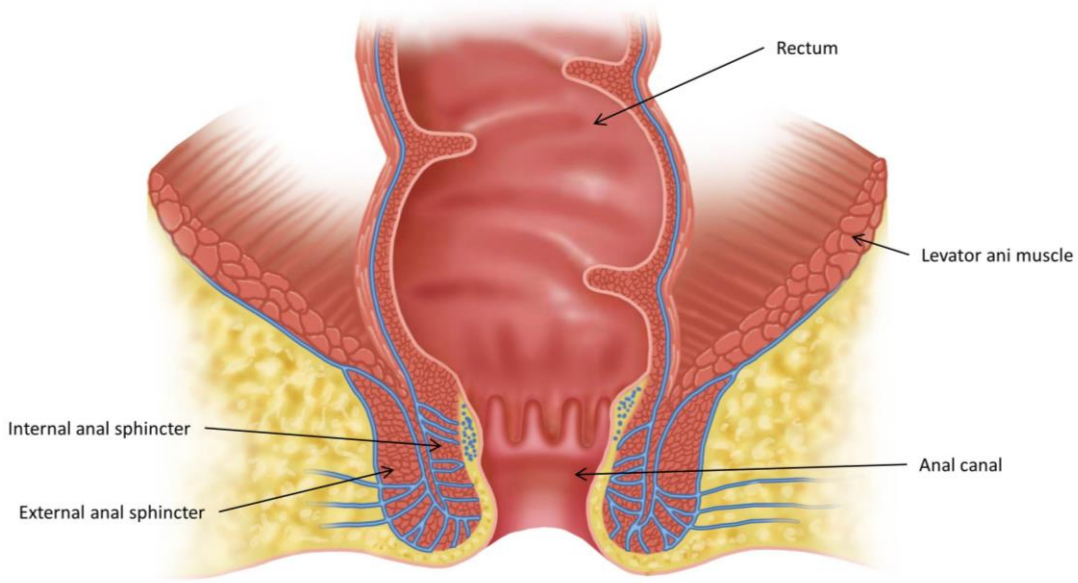
FI is often sub-divided in an attempt to classify symptomatology and determine pathophysiology. Passive FI occurs without the patients' knowledge that their bowels have opened; post-defaecation leakage is defined as passive FI temporally related to defaecation and urge FI occurs with the patient's awareness, causing them to rush to the toilet[6].

1.2 Applied anatomy of the anorectum

The rectum and anus comprise the most distal portion of the large bowel. The rectum, which serves as a reservoir for faecal material, is more proximal to the anus, begins at the upper level S3 and extends 12-15cm distally[7]. It is distinguishable from the sigmoid colon above, as the incomplete outer muscle layer or taenia on its surface have coalesced from three distinct bands to form a single longitudinal layer marking its surface[7]. Underlying this, the longitudinal muscle interlaces with circular muscle[5]. Below the rectum, the anal canal extends from the pelvic floor muscles to the anal verge, and is approximately 2.5 – 5cm in length (slightly longer in males than females)[7, 8]. The anal canal is surrounded by two muscles, the internal and external anal sphincters[7]. The internal anal sphincter is 0.3-0.5 cm thick and is a continuation of the inner circular smooth muscle surrounding the rectum, and the external anal sphincter

is 0.5-1cm thick and comprises an extension of the pelvic floor muscles[5, 7]. The two sphincters are separate and distinguishable morphologically[9]. The pelvic floor (levator ani muscle) is a striated muscle layer surrounding a central tendon, with openings for the urethra, vagina and rectum[8]. The levator ani muscle is comprised of 3 separate muscles; the iliococcygeus muscle, the pubococcygeus muscle and the puborectalis muscle, which work as one to support the pelvic organs, maintain continence and help co-ordinate defaecation[7]. This broad thin sheet of muscle originates from the inner surface of the lower pelvis[7]. At rest, there is a natural angle of approximately 90 degrees between the anus and rectum, maintained in part by the puborectalis muscle, which is considered the most significant portion of the levator ani in terms of continence, as it slings around the upper anal canal, inserting onto the pubis[5, 7]. Figure 1 is a schematic representation of the anatomy described.

Figure 1: Schematic coronal representation of anorectal anatomy



1.3 Innervation of the anorectum

Innervation of the anorectum is via the enteric, somatic, autonomic and central nervous systems[10]. The enteric nervous system is the intrinsic innervation of the GI tract, which comprises an outer myenteric plexus (which regulates smooth muscle activity) and an inner submucosal plexus (which influences secretory and absorptive functions, and local blood flow), and is modulated by the autonomic (sympathetic and parasympathetic) nervous system[10]. Afferent nerve fibres, located in GI tract epithelium and mucosa, which respond to distension, mucosal irritation and chemicals, are involved in local reflexes as well as conveying information centrally, via the enteric nervous system, prevertebral ganglia and vagus nerve[11]. Parasympathetic innervation to the hindgut i.e. descending colon, sigmoid colon and anorectum is via the pelvic nerves [10]. The pelvic nerves originate from the caudal S2, S3 and S4 nerve roots (forming nervi erigentes) which increase colonic motor activity and blood flow as well as providing an integral role in defaecation[7, 10]. Sensation of rectal distension is likely parasympathetically mediated[5]. Sympathetic innervation to the GI tract is from the thoracolumbar outflow (T5-L2), and fibres leave the spinal cord, pass through the paravertebral ganglia and relay to the coeliac and mesenteric ganglia, with most postganglionic sympathetic fibres terminating on the enteric nervous system[10]. Maintenance of anal tone, by internal anal sphincter contraction, is mediated by the sympathetic nervous system[10]. The sympathetic nervous system is responsible for inhibiting motility through the GI tract, and causing vasoconstriction via noradrenaline on enteric nerves[10].

The pudendal nerve provides innervation to the external anal sphincter and cutaneous sensation from the perianal area and perineum, but does not convey rectal sensation[10, 12]. With regards to the central nervous system, the medial prefrontal area and the anterior cingulate gyrus represent two areas that are involved in the timing and

initiation of defaecation at an appropriate time, with their effects over voluntary control being mediated through spinal pathways[10].

1.4 Physiology of continence and defaecation

Continence relies on the correct individual functioning of each of the component parts, namely the gastrointestinal tract and anal sphincter complex, brain and central nervous system and the autonomic and enteric nervous systems, and their correct, timely and co-ordinated actions together[13]. Factors contributing to the maintenance of continence are detailed in Table 1.

Table 1: Factors contributing to the maintenance of continence (Scott *et al.*[13])

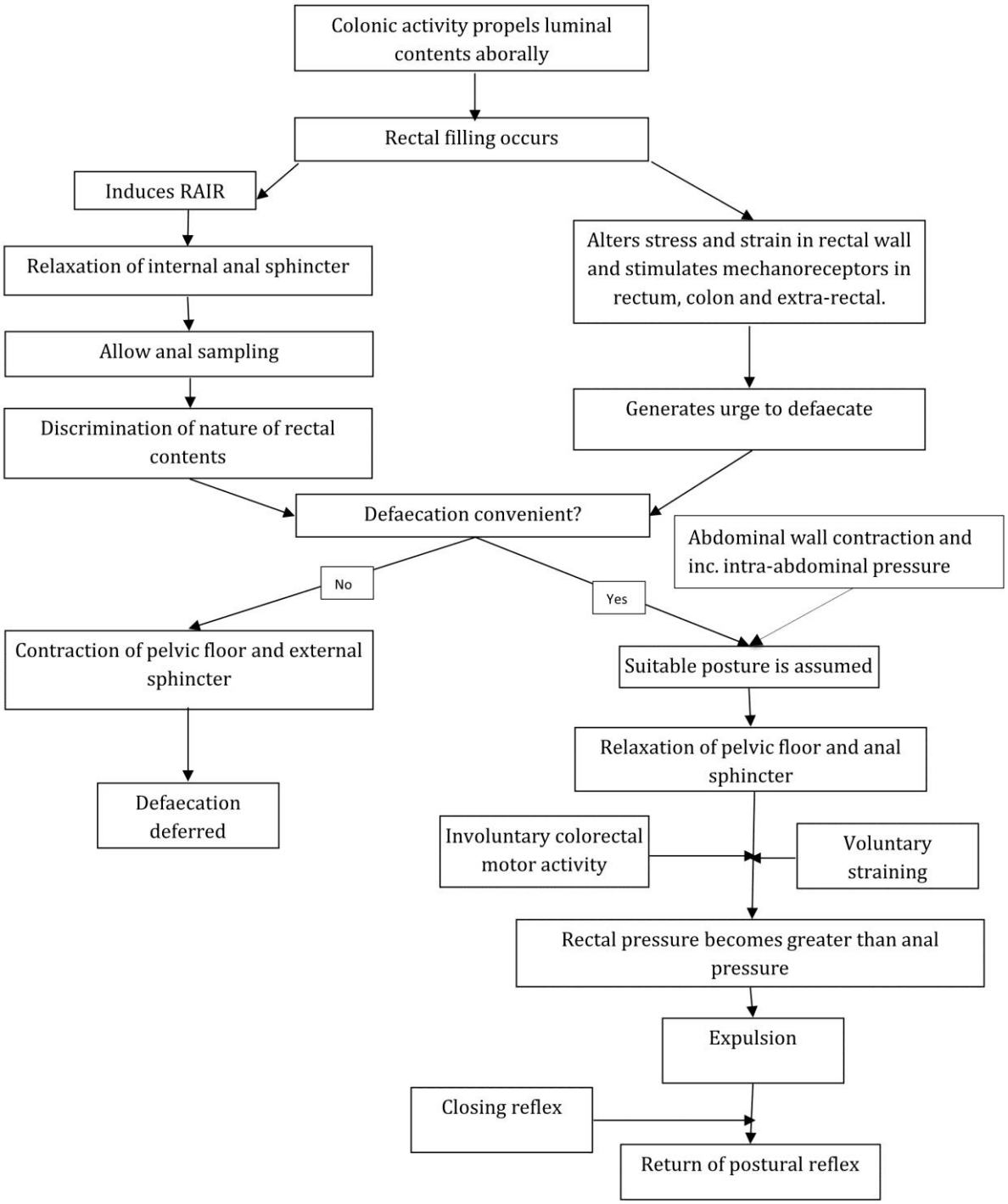
	Sphincteric	**Pelvic**	**Intestinal**
Structural	Anal sphincters Longitudinal muscle Vascular anal cushions and secondary mucosal folds	Levator ani Resting perineal position Rectal capacity	Intestinal length
Functional	Resting tone Squeeze increment Anal sensation, plasticity and motility Rectoanal inhibitory reflex Rectoanal contractile reflex	Levator ani contraction Anorectal angle Rectal tone, sensation and compliance Rectosigmoid motility Anorectal pressure gradient	Stool consistency and volume GI motility
Neurological	Satisfactory functioning of relevant nerves (pudendal nerve, sympathetic nerves, parasympathetic nerves, sacral somatic nerves, spinal afferent nerves, enteric nerves.		
Other	Central neurological integrity Psycho-behavioural factors Normal rectal evacuation		

The internal anal sphincter is responsible for the majority of the resting anal sphincter tone (between 55 and 85%)[12]. It comprises fatigue-resistant slow-twitch smooth muscle, which generates mechanical activity with a frequency of 15-35 cycles per minute and ultra-slow waves at 1.5-3 cycles per minute[14-17]. The external anal sphincter is comprised of striated muscle, which contains tonically contracting 'slow twitch' and phasically contracting 'fast twitch' fibres that are fatigable[8]. Though it contributes a little to anal resting tone[12] (reported as up to 30%[18]), its main function is to reinforce anal sphincter function during voluntary squeeze[5]. Pressures between 50 and 200mmHg can be generated in health[8]. The sphincter muscles alone cannot entirely close the anal lumen[19], but the blood-filled vascular tissue of the anal mucosa is thought to provide a further seal for the anus, contributing to a further 10 – 20% of the resting anal tone[18], and in addition to this the secondary anal mucosal folds provide a better seal[3]. Another feature that contributes to the maintenance of continence at rest is the acute angle maintained between the anus and rectum.

Once an urge is felt, continence is maintained by a combination of voluntary contraction of the external sphincter increasing intra-anal pressure, alongside contraction of the puborectalis muscle which creates a forward-pull causing the anorectal angle to become more acute[20].

The act of defaecation involves a complex interplay of features, which can be described as 4 distinct phases: [1] the basal phase, normal motor function of the colon and rectum prior to the urge to defaecate; [2] the pre-defaecatory phase, which leads to generation of the urge to defecate; [3] the expulsive phase, during which evacuation of the bowel contents occurs, and finally [4] the termination of defaecation[21]. This is described in Figure 2.

Figure 2: Flowchart to show the principal events during defaecation [21] .



The basal phase: Functions of the colon include water absorption, propulsion of faecal material, and the storage of faeces until a socially acceptable time for expulsion[21]. During any normal 24-hour period colonic motor activity is increased during the daytime hours, and maximally after waking and after eating[22-24]. Colonic motor activity

comprises brief, tonic contractions and prolonged, phasic contractions, which can be either propagating or non-propagating[24]. Net propagation is antegrade (aboral) though there is significant retrograde (oral) colonic activity also[21]. Faeces are delivered to the rectum, in which most motor activity at this point is in a retrograde direction, thought to contribute to maintenance of continence by acting as a 'brake'[21]. During this phase the pelvic floor muscles and external anal sphincter maintain tone in order to support the weight of the pelvic contents, and the anal canal is closed as described above[21]. So called 'anal sampling' is a physiological process whereby transient relaxation of the internal anal sphincter allows rectal contents to briefly enter the upper anal canal in order that the nature of the matter can be determined by the anal canal epithelium[25]. It is described as occurring 7 times per hour in health, and less frequently in patients with incontinence[25, 26]. Few data have been published on this theory since its first description in 1988, and some question whether this is an accurate representation of true physiology[27]. A reduction in internal anal sphincter tone occurs in response to rectal distension, and this is known as the 'rectoanal inhibitory reflex' (RAIR). Amplitude and duration of the anal relaxation increase with rectal volume and the reflex is mediated by the myenteric plexus[28]. The RAIR may facilitate the passage of flatus, but it is associated with a contractile response of the external anal sphincter, in order to prevent accidental passage of rectal contents[5].

The pre-defaecatory phase: This phase involves increasing motor activity of the colon, rectum and anus which culminate in a person perceiving the 'call to stool': a very important sensation in achieving normal defaecation[21]. The rectum is the predominant site that perceives defaecatory urge[21]; and gradual distension of the rectum causes a graded response, which begins with initial awareness of filling, followed by a constant sensation which then turns into a sustained urge to defecate and finally to an intense urge to defecate as the maximum tolerated pressure or volume is reached[29-31]. Normal defaecation relies on a combination of normal rectal afferent nerves and rectal wall

biomechanical properties in order that perception of rectal fullness and subsequent defaecatory urge are felt[32]. The pelvic floor muscles are in a state of continuous contraction to preserve continence, though it is thought that these muscles also have a role in generation of normal filling sensation and defaecatory urge perception through stretch receptors[21, 33]. During this phase, it is not known whether the 'anal sampling' reflex alters in any way, though it is likely that as rectal filling increases, the pressure exerted on the anal canal thus increases and increased contraction of puborectalis and the external anal sphincter are required to maintain continence[21].

The expulsive phase: This phase involves the active and conscious decision to evacuate the bowels following on from the presence of a defecatory urge, where a normal behavioural response to the urge to defaecate is integral[21]. During this process, a proportion of the colon as well as the rectum, empties[34]. Evacuation is facilitated by several factors; the adoption of an appropriate position; elevation of intra-abdominal and therefore intra-rectal pressure by straining; relaxation (or reflex inhibition) of the pelvic floor tonic activity resulting in straightening of the anorectal angle and finally relaxation of the anal canal[21]. Expulsion occurs and is maintained due to high intra-rectal pressure from straining, though it is thought that this is reinforced once defaecation has started, by a spinal reflex, which maintains propulsive force until the rectum is empty[35, 36]. Defaecation will continue to occur whilst intra-rectal pressure is higher than intra-anal pressure.

Termination of defaecation: This phase is under semi-voluntary control, with the cessation of straining or increased intra-abdominal and rectal pressure following the sensation of complete evacuation[21]. This in turn leads to involuntary contraction of the pelvic floor and external anal sphincter, which results in anal pressure again exceeding rectal pressure[21]. The passage of stool through the anal canal results in a traction force being applied to the external anal sphincter, which in turn causes a reflex increase in

external sphincter pressure. This 'closing reflex' is important in terminating defaecation and provides sphincter tone whilst the internal anal sphincter recovers from relaxation as a result of the RAIR[21]. Tone resumes in the pelvic floor muscles, which in turn increases the anorectal angle to its resting state. Defaecation is thus terminated.

1.5 Epidemiology of faecal incontinence

FI comprises a significant public health problem and causes much physical and psychological disability amongst those worst affected[2, 37, 38]. Results of clinic-based studies of FI cannot be extrapolated to estimate population prevalence of FI, and only true community-based studies will allow estimation of this. Unfortunately, due to the inherent strategic and economic difficulties associated with such studies, few epidemiological studies have been performed, making true estimation of the disease burden challenging.

Adding to this situation is the well-recognised but necessarily ill-defined population of 'silent sufferers', who have significant symptoms and associated physiological and psychological disability, but who never consult any medical professional. This may be due to any number of factors including embarrassment, failure of acceptance of the condition, or lack of knowledge that treatment strategies do exist, and it is estimated that this may account for between 55-85% of sufferers[4, 39, 40]. A study carried out in the USA estimated that two thirds of symptomatic patients did not report this condition to a physician[40, 41], similarly a study of women in the United Arab Emirates suggested that 60% of multiparous women with FI did not seek medical advice[42]. This study further questioned subjects with FI as to why they did not seek medical advice: 64.7% reported that this was due to embarrassment, 47.1% presumed it would resolve spontaneously, 31.3% thought this was normal and 23.5% chose self-treatment as they had low expectations of medical care[42].

This situation is not helped by the social taboo surrounding the subject of FI, especially in the UK, which has led to a relative paucity of published literature, and a distinct lack of media attention in terms of raising awareness and acceptance amongst the general public.

Differences in the reported prevalence of FI between studies may be due to a number of reasons. The main reason for differing prevalence seems to be the population studied with the most important factors being sex, age, health status and place of residence[2]. Another factor contributing to this is the lack of a standardised definition for 'FI', with some studies strictly reporting only FI symptoms as defined in 1.1 above, and other studies using the definition of 'anal incontinence' as in 1.1 above, which will clearly provide significantly differing estimations of disease burden.

Eleven studies have estimated prevalence of FI in the community by sampling all adults in a population [2, 38, 43-51]. These studies, which included between 500 and 7,196 subject, reported the prevalence of incontinence at between 1.9% [49] and 16.8% [51], although different definitions of 'incontinence', as described above, were used (Table 2).

1.5.1 Prevalence by country

The studies described above comprised three studies from the USA, three studies from Australia, one from Brazil, one from Germany, one from New Zealand, one from France and one from the UK and it seems that there are no substantial geographical differences in the prevalence of FI. Many other studies in the literature have estimated rates of FI in different countries and these are summarised in Table 2.

Table 2: Studies of rates of FI in different countries (adapted from Nelson. (53)).

Reference	Country	Population	Number of subjects	Prevalence
MacLennan *et al.* 2000	Australia	Household survey	3010	2.3% men; 3.5% women >15 years old
Lam *et al.* 1999	Australia	Age >18 yr	618	15% (M= 20%; F = 11%)
Kalantar *et al.* 2002	Australia	Age >18 yr	651	2% solid; 9% liquid (F>M)
Santos *et al.* 2014	Brazil	Age >18 yr	2162	3.6% (F>M)
Siproudhis *et al.* 2006	France	Household community survey	7169	16.8%
Giebel *et al.* 1998	Germany	Age >18 yr	500	4.8%
Lynch *et al.* 2002	New Zealand	Age >18 yr	717	9.8% for solid; 12.7% for liquid; 64% gas
Thomas *et al.* 1984	UK	Community	4844	1.9%
Drossman *et al.* 1993	US	Market mailing	5430	7% soiling; 0.7% to faeces
Nelson *et al.* 1995	US	Wisconsin households	6959	2.2%; 63% of whom were women
Whitehead *et al.* 2009	US	Household survey	4308	8.3% (M=F); 1.6% solid stool
Denis *et al.* 1992	France	Age>45 years	1100	11%, 6% to faeces; 60% of whom were women
Perry *et al.* 2002	UK	Age >40 yr	10 116	1.4% (M=F)
Talley *et al.* 1999	US	Age >65 yr, at home	328	3.7% (M>F)
Bharucha *et al.* 2006	US	Olmsted County women >20 years old	2800	12.1% in females; increasing with age
Melville *et al.* 2005	US	HMO population 30-90 years. Washington State	3536	7.7% in females
Quander *et al.* 2005	US	Chicago Health and Ageing Project >65 years old	6158	6.9%; associated with age (M=F)
Varma *et al.* 2006	US	Population based study of females >40 years	2109	24% in females
Nygaard *et al.* 2008	US	Survey of women	1961	9% in women
Matthews *et al.* 2013	US	Women aged 62-87 years	64, 396	11.5%

1.5.2 Prevalence by sex

There is on-going debate regarding the differences in prevalence of incontinence between males and females. Perry *et al*. have suggested differences may exist due to the age of the population studied, may represent differences in referral pattern and consultation behaviour, indeed it has been shown that women are more likely to report symptoms than men[2], or may represent differences in aetiology[52, 53]. The differences between sexes may also be accounted for by considering the definition of incontinence used. The suggestion being that in those studies that define 'anal incontinence' prevalence, a higher preponderance of women can be explained by the association between childbirth and a higher rate of flatus incontinence[53]. Alternatively, Maddoff *et al*. have suggested that the differences may be explained as most reported clinical series have a female preponderance whereas epidemiological studies are those which report equal distribution between the sexes, and this points more towards consultation behaviour than any other reason[4].

With regard to FI, some studies found equal prevalence in both sexes, for example the UK based study of 10,116 adults over the age of 40 years, calculated the prevalence of FI to be 6.2% in men and 5.7% in women, i.e. with no differences between sexes[53]. Other studies have found a higher prevalence in women, for example the Australian study of 3,010 adults found higher rates of flatus and FI in women than men (10.9% vs 6.8% and 3.5% vs 2.3% respectively)[43]. Another Australian study of 651 subjects found that 55% of those suffering FI were women (although no significance was attached to this)[45]. A US study of 6, 959 individuals found 63% of those suffering FI were women, and indeed this was an independent risk factor for incontinence[2]. Conversely, other studies have found higher rates of faecal incontinence in men, for example the Australian study of 618 subjects (259 males) found prevalence significantly higher in men than women (20% vs. 11% (p=<0.015)[44]. Other studies have found equal

prevalence in both sexes [54-57], higher prevalence in men[55, 57, 58] and higher prevalence in women[39, 59, 60]. However all of these studies have concentrated only on the elderly population, which is a separate epidemiological factor in itself.

1.5.3 Prevalence by age

Many studies have concentrated on the prevalence of incontinence amongst older individuals who are not institutionalised. Prevalence of FI in 6 studies with subjects over the age of 50 years ranges from 3% to 16.9%[39, 54, 55, 57, 59, 61]. Of these studies, 3 found an increased prevalence of FI with age[54, 57, 61] (although one of these studies only included women[61]), one found an increased prevalence with age in men but not women[59] and the other reported no significant change with age[39]. Of the studies considering the whole population, the UK based study of 10, 116 adults over the age of 40 years found a steady increase in prevalence with age in terms of both frequency of leakage and severity of leakage episodes (0.9% adults between 40-64 years and 2.3% adults aged 65 years or over)[53]. Similarly an American community based study that estimated the prevalence of anal incontinence in 6, 959 adults to be 2.2%, found a majority of sufferers over the age of 65 years (greater than two thirds)[2]. A further epidemiological study of 3, 010 subjects in Australia found an association between all types of pelvic floor disorders and age in both males and females[43].

Most studies seem to agree that prevalence and severity of FI increase with age, and as populations age, comorbid disease becomes a significant component of incontinence risk[39, 53].

1.5.4 Prevalence amongst institutionalised individuals

The prevalence of FI amongst the institutionalised elderly population is undisputedly higher than the general elderly population, with four studies quoting prevalence estimates between 46% and 54.4% in sample sizes ranging from 447 to 18, 170

subjects[62-65]. Indeed FI prevalence is disproportionately high amongst those with severe mental and physical disability, and although FI is often attributed as the reason for older people becoming institutionalised[53, 66, 67], it seems the evidence to back up this claim is limited[68-70]. The reasons for such high prevalence amongst institutionalised elderly may be attributed to poor functional status, impaired cognitive ability or dementia and limited mobility[60, 71]. There is also evidence to suggest rates of incontinence correlate with length of time spent in a nursing home [63].

1.5.5 Prevalence by ethnicity

There is some literature regarding FI and race. Varma *et al.*, reported no difference in prevalence of FI in women by race in a large population based study in the US[72], however another community-based US study of women has reported that FI is almost twice as common in white women as opposed to black women[73]. This may, at least in part, be explained by the apparent reduced risk of anal sphincter injury amongst Afro-Caribbean women as compared to Caucasian or Hispanic women reported in two studies[74, 75]. Another study found Asian, Indian and Pilipino women to have an increased risk of obstetric anal injury[76].

1.6 Pathophysiology of faecal incontinence

Since the maintenance of continence relies on the correct individual functioning of each of the anatomical components listed above, and their correct, timely and co-ordinated actions,[13] failure of the individual functioning of any of these components or of their co-ordinated action, could result in FI. Many people may exhibit more than one pathophysiological mechanism. Pathophysiological mechanisms for FI can be physiological or psychological (Table 3).

Table 3: Pathophysiological mechanisms for faecal incontinence.

Physiological Factors
Failures of internal anal sphincter, external anal sphincter or puborectalis muscle Abnormal rectal sensation or rectal compliance Abnormal stool consistency e.g. diarrhoea Impaired mental faculties Impaired mobility
Psychological Factors
Anxiety and depression

1.6.1 Physiological factors

1.6.1.1 Failures of anal sphincter complex and puborectalis muscle

Controlled studies report anal sphincter weakness as the most commonly identified abnormality in incontinent patients. In older women with FI, a study reported approximately 40% had reduced anal resting pressure and 80% had reduced squeeze pressure [77].

Internal anal sphincter dysfunction may be characterised by exaggerated spontaneous relaxation of the internal anal sphincter (sampling reflex)[78] or decreased resting pressure [77, 78]. Decreased anal resting pressure may be as a result of a discrete defect in the internal anal sphincter (e.g. following traumatic vaginal delivery) or a generalised thinning of the muscle (e.g. with age). External anal sphincter weakness may result from sphincter damage (e.g. by surgery), neuropathy (generalised or specific to pudendal nerve) or myopathy. Failure of puborectalis to maintain continence may occur in patients with excessive perineal descent, who have a more obtuse anorectal angle, impairing the flap valve that normally maintains continence when intra-abdominal pressure increases.[79]

Few studies have evaluated the pathophysiology of FI in men, [80-82] which indeed is often associated with normal sphincter function.[81, 83] In the presence of iatrogenic

injury to the sphincters, pathophysiology is similar to that in females, however where this has not occurred, FI may be associated with dyssynergic defaecation,[84] high anal resting pressure trapping stool which is subsequently expelled without the usual control, causing soiling,[85] or isolated weakness of the internal anal sphincter.

1.6.1.2 Abnormal rectal sensation or rectal compliance

Abnormalities of the rectum, including sensation and compliance can lead to FI. If rectal sensation is reduced, an episode of FI may have occurred before the external sphincter has contracted [30, 78, 86]. Alternatively, if a patient has decreased rectal sensation and increased rectal compliance the resultant faecal retention may then lead to overflow incontinence. Conversely, increased rectal sensation may result in symptoms of urgency, and associated urge faecal incontinence [77, 87].

1.6.1.3 Other factors

In addition to the problems listed above, FI may also be a result of abnormal stool consistency e.g. diarrhoea, impaired mental faculties or immobility (resulting in an inability to reach the toilet at the correct time).

1.6.2 Psychological factors

FI has a profound effect on emotional, social and psychological function, and is significantly associated with anxiety and depression [88]. Higher depression scores are associated with more severe quality of life impairment in patients with FI [89]. Other functional gastrointestinal disorders have shown an association between psychological stress and alteration of the brain-gut axis, and this is likely to also occur in FI.

1.7 Risk factors for faecal incontinence

In a minority of cases, there is a clear and direct cause for a person to suffer FI, for example internal anal sphincter division during a lateral sphincterotomy for non-healing fissure. For many people however, there is no obvious temporal relationship. FI may come on years after an apparently uneventful vaginal delivery; the association between the event and the symptoms is less clear, and indeed the event may be just one component of a multifactorial aetiology. Structural sphincteric causes for FI are relatively easy to investigate, however in many people who suffer FI no structural problem is evident. Risk factors are definable entities that place one individual at greater risk of developing a condition than another individual who has not been exposed to that same factor[13]. Many risk factors for FI have been identified (Table 4). Unfortunately, there are few epidemiological studies that have systematically reviewed all potential risk factors for FI, with most studies instead being clinic-based and so not generalisable to a whole population. In truth, it is likely that most patients (up to 80%) have a combination of factors, the sum total of which has contributed to their symptomatology[78, 90].

Table 4: Risk factors for faecal incontinence

Anal sphincter weakness
Traumatic: Obstetric, surgical (e.g. haemorrhoidectomy, internal sphincterotomy, fistulectomy) Non-traumatic: Scleroderma, internal sphincter degeneration of unknown aetiology
Neuropathy
Peripheral (e.g. pudendal) or generalised (e.g. diabetes mellitus)
Pelvic floor deficiency
Rectal prolapse Increased perineal descent
Diarrhoea
Irritable bowel syndrome, post-cholecystectomy diarrhoea Faecal retention with overflow Inflammatory bowel conditions and anorectal surgery as listed below
Problems of rectal capacity
Inflammatory conditions: Radiation proctitis, Crohn's disease, ulcerative colitis Anorectal surgery (e.g. ileo-anal pouch or anterior resection)
Central nervous system disorders
Dementia, stroke, brain tumour, multiple sclerosis, spinal cord lesion Psychiatric diseases, behavioural disorders

1.7.1 Faecal incontinence in women

1.7.1.1 Obstetric injury

Obstetric injury is a major contributor to FI in women, indeed obstetric trauma is often cited as the most common cause of anal sphincter injury[91-94]. Obstetric anal sphincter injuries (OASIS) are classified by the Thakar and Sultan Classification of Perineal Trauma from first to fourth degree tears[95] (Table 5).

Table 5: Classification of perineal tears[95]

Tear classification	**Description**
First degree	Only vaginal epithelium or perineal skin involved
Second degree	Involves perineal muscles but not anal sphincter
Third degree	Disruption of the anal sphincter muscles. Divided into: • 3a: <50% thickness of external sphincter torn • 3b: >50% thickness of external sphincter torn • 3c: Internal sphincter also torn
Fourth degree tear	3c tear in which anal epithelium also disrupted

It is reported that 85% of women sustain some perineal trauma during vaginal delivery[96], and the mechanisms for this are twofold, namely structural i.e. direct sphincteric damage via third and fourth degree tears, or neurological i.e. injury to the pudendal nerve from the foetal head[97-99]. More recently it has been postulated that it may not just be injury to the pudendal nerve that results in subsequent symptomatology, but that the inferior hypogastric plexus may indeed be damaged. This would result in damage to intrinsic and extrinsic nerves innervating pelvic viscera thus resulting in pelvic floor dysfunction (and the development of faecal urgency and altered sensory function)[100]. Most patients were thought to have 'neurological' FI[101] until the advent of endoanal ultrasound scanning (EAUS) which enabled morphological study of the sphincter. It is now believed that isolated neuropathy as a cause of incontinence only occurs in about 10% of cases[102] whereas a structural sphincteric injury is identified in the majority[93, 103, 104], however in truth it is likely that in most patients there is a combination of both.

Many studies have shown a strong association between OASIS and symptomatic FI, although some women who suffer no occult sphincter injury do seem to suffer FI[105]. Nine studies[92, 106-112] in which sphincter integrity postpartum was assessed with EAUS to assess the relationship between new sphincter defects and symptoms of FI have been summarised[13]. The median study size was 96 (range 35 – 197), and a new sphincter defect was observed in a median of 29% (range 20-45%) of women. A median of 44% (range 0-75%) women had a newly symptomatic defect compared to a median of only 1.3% (range 0-6.8%) women who were newly symptomatic with FI but had no sphincter defect identified. This summary reports that the studies show a median of 8.5% (range 0-46%) of the sphincter defects are isolated to the internal anal sphincter, a median of 68.5% (range 18-85%) are isolated to the external anal sphincter and a median of 24% (range 5-36%) involve both the internal and external

anal sphincters. A summary of 8 studies[92, 106, 107, 109-113] confirms that it is most commonly the external anal sphincter that is disrupted during childbirth[114].

Meta-analysis of 5 studies[92, 106, 108, 113, 115] which report the incidence of new OASIS (third and fourth degree tears) following vaginal delivery in a total of 717 women calculated the incidence as 26.9% after first vaginal delivery and 8.5% after subsequent vaginal deliveries, estimating that a total of 35.4% of multiparous women have OASIS[116]. Thirty per cent of the women with sphincter injury in these studies reported symptoms of anal incontinence. Conversely 3.4% of women who had no discernible sphincter injury still experienced symptoms of anal incontinence[116]. Therefore the incidence of anal sphincter defects and symptoms of FI is 29.7% and the calculated probability of postpartum FI being due to sphincter defect is 76.8% in primiparous women and 82.8% in multiparous women[116]. This said, it is worth noting that the length of follow-up for the women in all these studies was short (<1 year after delivery).

A prospective study by Pollack *et al.* involved 242 nulliparous women whose medical history, bowel habits and symptoms of anal incontinence were ascertained during the puerperal period, and who were asked again about bowel habits and anal incontinence at 5 months, 9 months and 5 years following vaginal delivery[98]. Fifteen per cent of women (36 women) had a recognised and treated sphincter injury at their index delivery and 44% (16 women) of these had anal incontinence at 9 months follow-up, which by 5 years had increased to 53% (19 women). Of the 206 women who had no sphincter injury detected at index delivery, 52 (25%) reported some degree of anal incontinence at 9 months, and at 5 years this had increased to 66 women (32%). Nine of the 36 women with a sphincter tear at first delivery, who had no additional childbirths, reported an incidence of incontinence of 44% (4 women) at both 9 months and 5 years follow-up. Of the remaining 27 women who did have subsequent

childbirths, 12 (44%) reported incontinence at 9 months and this had increased to 15 (56%) at 5 years. Of the 205 women who had no sphincter injury initially, 44 had no subsequent childbirths, and at 9 months 9 (20%) reported anal incontinence which increased to 11 (25%) at 5 years. Of the 162 women who did have subsequent childbirths, the rate of incontinence reported at 9 months was 27% (44 women) at 9 months and 34% (70 women) at 5 years. On multivariate logistic regression this study found maternal age, sphincter tear at first delivery and subsequent childbirth were independent risk factors for developing anal incontinence. The presence of anal incontinence after first delivery was the strongest risk factor with the odds ratio of incontinence at 9 months leading to incontinence at 5 years being 4.3 (95% CI 2.2 – 8.2); this increased to an odds ratio of 7.8 (95% CI 1.6 – 8.8) in the presence of a sphincter tear at the first delivery. This study did not assess for the presence of anal sphincter injury by EAUS, which may indicate an underestimate of the number of occult injuries and may account for the rate of incontinence in those without diagnosed sphincter injury. Alternatively this rate may be due to neurological injury sustained during uncomplicated childbirth[92, 117].

Many further studies have shown other factors which increase the likelihood of FI following vaginal delivery, and these include all forms of instrumental-assisted delivery[118, 119], unassisted delivery at home, prolonged second stage of labour (indeed one third of women who have a second stage of labour lasting greater than 4 hours will sustain an OASIS)[120, 121] large birth weight (>4kg)[76, 118, 122], large head circumference, maternal obesity[123, 124] and increasing maternal age[92, 122, 125]. Factors which have been identified as increasing risk of OASIS, and therefore also increasing likelihood of FI include midline episiotomy, first vaginal delivery, shoulder dystocia and persistent occipito-posterior presentations[92, 122, 126-128]. Epidural anaesthesia has also been linked to an increased risk of OASIS[102, 129]. It is worth noting that although many studies find

overlap in the risk factors associated with subsequent FI and/or OASIS, there is rarely agreement that all of these are factors in all studies.

Women often present with FI some 2-3 decades following the vaginal delivery in which they sustained an OASIS, increasing the likelihood that the involvement of another factor or factors is required to cause overt symptoms[99]. It may be that neuropathy sustained during childbirth may be worsened by other factors, such factors may be for example multiparity[108, 130-132], chronic straining at stool[133-135], or advancing age[136].

1.7.1.2 The effect of Caesarean section

It is interesting at this point to consider whether elective Caesarean section (CS) is protective against the risks of FI, given vaginal delivery, especially complicated vaginal delivery, is a risk factor. Whilst significant literature exists in this area, often comparisons between vaginal delivery and CS do not consider that elective and emergency CS should not be categorized together.

A recent Cochrane review found no demonstrable benefit of elective primary CS in the preservation of anal incontinence[137]. This review was based on 21 reports, all of which were non-randomised, and included over 31 000 women. The report acknowledges that the evidence in this area is 'less than optimal' and that a study to randomise average risk pregnancies into vaginal vs CS deliveries would significantly improve this.

A further study from Sweden, published in 2014, found the prevalence of late FI and anal incontinence (20 years after delivery) were higher after vaginal delivery compared to CS delivery, offering some evidence of a protective effect of CS[138].

In truth, a properly designed RCT of elective CS vs vaginal delivery would be the only way to answer this question, however it is likely that huge crossover would exist

between groups, based on medical decision making and personal choice, making interpretation of results difficult.

1.7.1.3 Other factors in women

A study of 475 females with FI explored the relationship between symptoms and the occurrence of four previously proposed risk factors: obstetric events, anal surgery, pelvic surgery and neurological factors[6] . It found that although the overwhelming risk factor was indeed childbirth (91%), with at least one vaginal delivery reported as complicated in 338 (78%) (perineal trauma [episiotomy or tear], forceps or ventouse extraction), 67% women did report more than one risk factor, namely pelvic surgery (most commonly hysterectomy) in 153 and anal surgery in 90 (19%)[6]. However in the 150 females reporting only a single risk factor, obstetric history was by far the most common (124 or 86%) and of those, whilst most had complicated vaginal deliveries (105), 16 patients reported that these vaginal deliveries were completely uncomplicated[6] .

A population-based study of over 2, 000 females over the age of 40 years showed that independent risk factors to developing FI in the previous year included obesity, COPD, irritable bowel syndrome, urinary incontinence and colectomy[72]. In the same study, risk factors associated with women having FI episodes on a monthly or more frequent basis included (in addition to those above), age, diabetes, parity and cholecystectomy[72]. Previous studies have linked obesity to FI[139, 140]. Diarrhoea has also been previously been established as an independent risk factor for FI[141], with this often linked to other medical conditions in which an association with FI has been made, for example diabetes[66, 142, 143], irritable bowel syndrome[144] previous cholecystectomy[145] and colectomy[144]. Urinary incontinence has been found an independent risk factor for FI in women, which increases the likelihood that childbirth and associated damage to the

pelvic floor is a factor in FI, since it is believed that urinary and faecal incontinence share an aetiology[72].

Hysterectomy, oestrogen use and menopause were also found to be independently associated with FI[72]. At odds however with other literature, this study by Varma *et al.* found hysterectomy to confer a decreased risk of FI. Another group found an increased risk of FI after hysterectomy with oophorectomy[141] and one other study found no link[139]. Certainly within our practice, a significant number of women seem to make this association, but this does not necessarily correlate with direct causation. The large population based study found a 30% increased risk of FI in women using oestrogen replacement therapy[72], and this is in agreement with published randomised controlled trial data regarding an association with oestrogen and worsening of urinary incontinence[146, 147]. The mechanism for this is, however, unclear. The increased risk in post-menopausal women found in the population study has not been replicated by others, however it is difficult to know whether this is due to a lack of awareness of this as a potential risk factor[72].

It is likely that all of the above associations are explicable and link to one of the pathophysiological classification discussed in Section 1.5. For example, chronic cough (COPD) and obesity cause increased pressure on the pelvic floor; diabetes, colectomy, cholecystectomy and irritable bowel syndrome may increase intestinal motility, resulting in diarrhoea; and diabetes, age, and parity may all have an effect on the neurological system, causing generalised or specific pudendal neuropathy[72]. It is difficult however to know whether many of the specific (e.g. diabetes) and non-specific (e.g. ageing) associations made with increased risk of FI result through their general effect on mobility and ability to carry out the activities of daily living, and this too makes cause-effect associations even more difficult to define[114].

1.7.2 Faecal incontinence in men

Since the primary cause of FI in women is often cited as childbirth, aetiological factors associated with FI in men have to be different. Fewer data exist to address specific aetiological factors in men, however, it is likely that many factors are overlapping with females.

A study by Kim *et al.* reviewed the medical notes of 404 male patients with FI in two groups, namely those under the age of 70 years (Group A) and those aged 70 years or over (Group B), in order to ascertain likely aetiological factors[148]. Of these patients, 321 (79.5%) had a history of at least one anorectal disease that may affect continence, (167 (82.3%) in group A and 154 (76.6%) in group B). 234 (57.9%) of the group had undergone at least one procedure that might affect faecal continence (which comprised 121 patients (59.6%) from group A and 113 patients (56.2%) from group B). The most common prior anorectal diagnoses amongst patients in group A which may have affected anal continence included perianal sepsis, perianal trauma, congenital disorders, HIV infection and anal cancer. However, in group B the most common prior diagnoses were prostate cancer, neurological diseases and colon cancer. In group A, the most common procedures which might have affected continence were prostatectomy or proctocolectomy, fistulotomy, pull through operation for imperforate anus, anal wide excision and radiation therapy for anal cancer, whereas in group B, the most common procedure was radiation therapy for prostate cancer. These results may seem as one would expect given the prevalence of certain diseases at a given age. This study did, however, fail to consider any other factors that may be associated with FI.

One of the above mentioned publications also considers the aetiological risk factors associated with FI in male patients by screening the medical history for the presence of three proposed risk factors (anal surgery, pelvic surgery, neurological factors)[6]. Of the 154 males included in the study, 120 (79%) had histories which contained volunteered

potential risk factors and of those, the most commonly reported factor by far was anal surgery (50%), which comprised mostly haemorrhoidectomy followed, in terms of risk, by fistula surgery and sphincterotomy for anal fissure. In incontinent males, usually only a single risk factor was volunteered (76 males or 50%), which was anal surgery in 45 (59%). This study did not document the presence or absence of other more general risk factors, for example diabetes or obesity, since these were not routinely screened for.

1.7.3 Faecal incontinence and its association with defaecatory disorders

Faecal impaction is an important risk factor in FI, and this is a well-described phenomenon in the elderly population[4, 66] and amongst children[66, 103, 149]. Faecal impaction may result from incomplete rectal emptying or as a consequence of other factors such as physical immobility, poor diet and fluid intake, and constipating medications[4]. Such faecal impaction may result in overflow incontinence as liquid stool seeps around the stool bolus[150]. More recently, an association has been made between co-existent defecatory disorder and FI in the absence of faecal impaction[151]. Defecatory disorder refers to difficulty evacuating stool from the rectum in a patient with chronic or recurring symptoms of constipation[152]. Causes can be structural (e.g. due to rectocoele or intussusception) or functional (e.g. inadequate defaecatory propulsion and/or dyssynergic defaecation). This link is also described amongst post-partum women, where up to 40% of patients suffer with coexistent symptoms[153]. Although the mechanism underlying this is not completely clear, it is possible that FI and defecatory disorder share a common pathophysiology.

1.7.4 Summary

The difficulty with attribution of aetiology to any individual suffering from FI is that it is often impossible to say with any degree of certainty why this pathophysiology has

arisen. Maintenance of continence relies on a complex interplay between many sensory and motor functions, and there is often a degree of compensation by different mechanisms to maintain continence in the event of dysfunction of one aspect of continence. Whether the balance tips towards symptoms, i.e. FI, involves a combination of one or more aetiological factors interplaying with inability of other mechanisms to compensate.

Although there is much published literature in this area, no study could consider every possible risk factor to define a relative risk, especially since direct causation can rarely be allocated. Studies which only use univariate analysis are particularly susceptible to this, since possible confounding factors such as age, BMI, parity and common medical conditions are not included in the analysis[72]. Long-term prospective detailed studies of large cohorts of patients are required in order to improve the strength of evidence, however with such studies being hugely costly and impractical the reality of the situation may be that the literature in this area will continue to have limitations.

1.8 Unmet clinical need associated with faecal incontinence

FI is not a life threatening condition, but the personal impact of incontinence is profound. It can cause medical morbidity (decubitus ulcers, urinary tract infections) and involve significant cost to those involved, causing many to withdraw from society and remain in close proximity to a toilet at all times to avoid incontinent episodes[4, 154]. The impact that FI has on quality of life cannot be underestimated as it causes social and psychological disability, and often leads to people suffering from stigmatisation and social exclusion[52, 155-158].

Quantifying FI can also be troublesome, as can assessment of disease progression or improvement. Whilst bowel diaries (Appendix 1) and scoring systems are the most commonly used methods, each has its limitations. These are discussed in later chapters.

The most commonly used scoring systems for FI are the St Marks' Continence Score[159] (Appendix 2) and the Cleveland Clinic Incontinence Score[160](Appendix 3).

1.8.1 Quality of Life

Impact of FI on quality of life (QOL) has most often been studied in the clinic, rather than in the community[154, 161] and many studies are focused on a particular patient population, resulting in minimal data being available to help understand the personal and economic impact of FI on the population as a whole[154]. One US based population survey assessing effect of FI on quality of life amongst 2, 800 women found that in the 503 symptomatic patients, FI had a moderate or severe impact on one or more QOL domains (activities at home, activities away from home and travel) in 23% of women, with the impact of QOL related to symptom severity i.e. 6% of women with mild symptoms, 35% of women with moderate symptoms and 82% of women with severe symptoms reported a moderate or severe impact on one or more QOL domain[162]. Similarly, this study found that self-reported health status was also associated with the prevalence of FI ($p<0.001$), the severity of FI ($P<0.0001$) and the impact of FI on QOL averaged across all domains ($p<0.001$). Similarly, a UK population-based study reported that 51.7% of those reporting major FI found this problem to have 'a lot' of impact on their quality of life, compared to a rate of 16% in those with minor FI and only 2.9% in those with rare or no FI[53]. Indeed FI remained significantly associated with a large impact on quality of life even when adjustment for other bowel symptoms had been made[53]. A large impact on quality of life was significantly more frequent in both those with major incontinence (odds ratio 12.4) and minor incontinence (odds ratio 2.5) compared to those with rare or no FI[53]. Another UK based study of 2, 818 individuals over 65 years old found a 4-fold increase in anxiety and a 5-fold increase in depression in those who had FI compared to those who did not. The same study also reported that 59% of those with FI described themselves as severely disabled compared to 16% of the study population without FI[39]. There seems little doubt that FI

has a huge impact on the quality of life of those who suffer, and this effect worsens with severity of symptoms.

1.8.2 Health Economics

In order to estimate healthcare costs, many health economists will calculate direct costs, indirect costs and consequent costs[154]. Direct costs include those for delivering a treatment, for example healthcare provider costs, hospital fees, medications, continence pads or appliances, and transport costs[154]. Indirect costs are those to the individual and ultimately society as a whole from work absenteeism, impaired performance at work, and those who seek alternative professions due to symptoms[154]. Consequent costs involve those involved with treating sequelae of a condition, for example the costs associated with treating skin breakdown arising due to FI[154].

Estimation of the direct economic costs of FI is difficult due to the few data available. It is estimated that combined urinary and FI in adults account for 2% of the total UK healthcare budget with an annual NHS spend in excess of £500 million[163]. One study of FI amongst institutionalised patients in Ontario Canada has calculated the mean time spent each day dealing with FI is 52.5 minutes per patient and the total annual cost of incontinence per patient to be $9, 771[62]. Another study of urogynaecological patients in Minnesota estimated lifetime charges to patients with FI secondary to obstetric injury at $17, 166[164]. Although medical and surgical costs associated with interventions are easily determined, calculating the economic impact of FI on a whole population is difficult due to differing study populations, for example differing ages and living arrangements, variations in treatment strategies between physicians and institutions and differences in associated costs between different regions and countries[165].

Indirect costs associated with FI are even more difficult to calculate, but are believed to be large. In the USA these extend to hundreds of millions of dollars per year[154]. A survey of 5, 400 US adults found that compared to 4.2% of asymptomatic individuals,

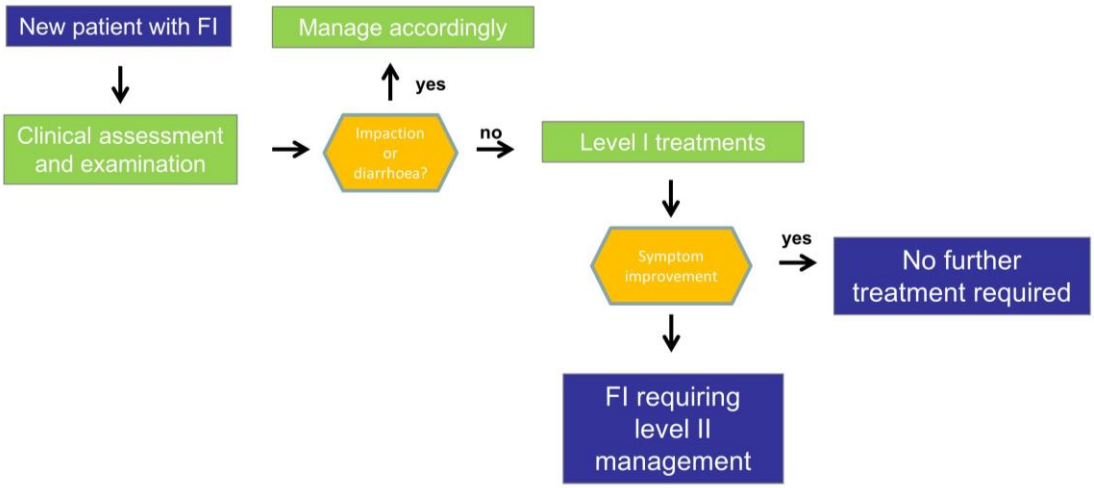
13.2% of those with any FI and 29.4% of those with large-volume FI considered themselves too sick to attend work or school, with those suffering large-volume FI missing an average of 50 days in the past year compared to 4.9 days in asymptomatic individuals[38].

It is clear that FI represents an area of unmet clinical need with attendant high economic costs to patients, the NHS and the economic function of the country as a whole[163].

1.9 Management of faecal incontinence

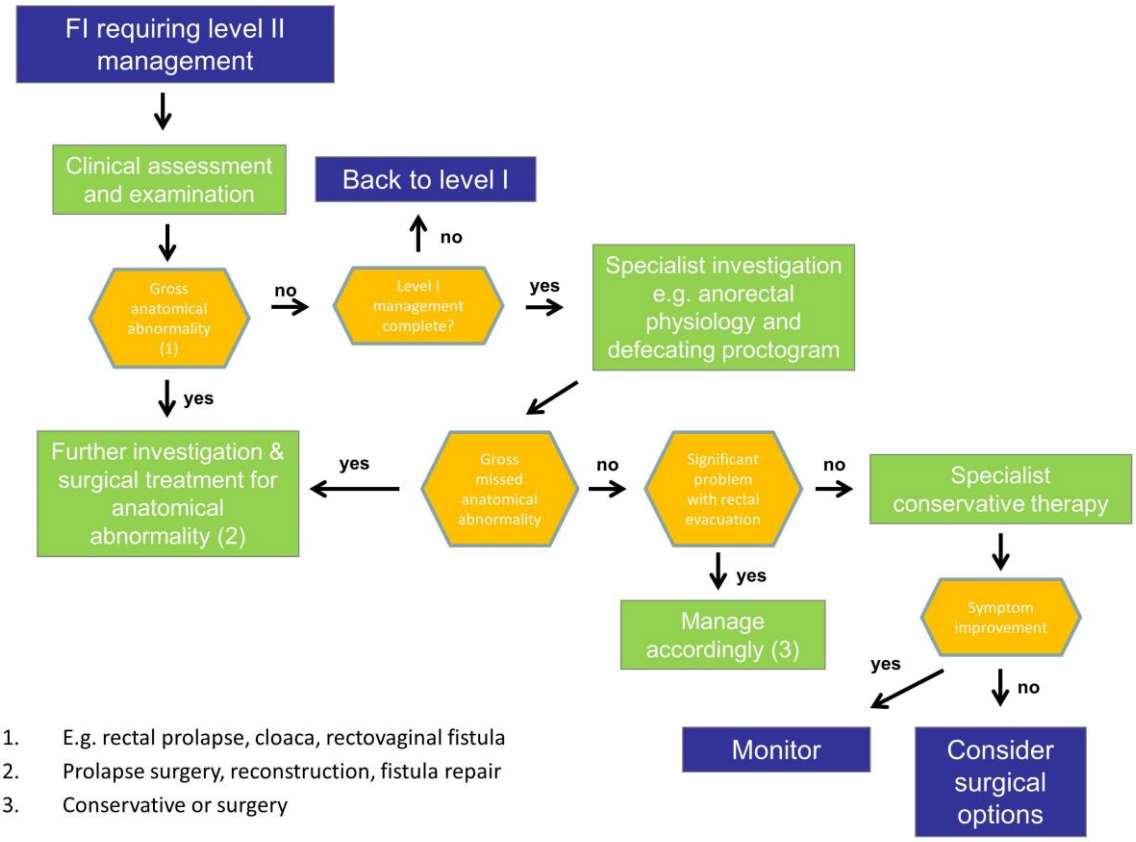
Management of FI can be challenging due to a combination of its high prevalence, aetiological heterogeneity and a lack of widespread expertise. NICE have published a 'NICE Pathway' for the management of FI amongst adults, which brings together all NICE guidelines. In addition to this, there is guidance from the International Consultation on Incontinence[166] and the Rome Foundation[167]. Our department has devised a basic algorithm of care for FI patients, which encompasses guidance from all three sources. It consists of initial basic assessment and treatment of patients (Level I) (Figure 3) and followed by appropriate management strategies for specific conditions, the use of specialist tests and more specialist conservative therapy (Level II) (Figure 4). Patients should be managed in a dedicated unit equipped with the appropriate facilities, expertise and full multidisciplinary team. Following thorough and detailed history, examination and appropriate investigations, all patients suffering with faecal incontinence should follow an initial pathway of condition-specific first line conservative interventions, singly or in combination, prior to specialised treatment including any invasive or surgical options [168, 169].

Figure 3: Algorithm of care for Faecal Incontinence: Level I



Level I Treatments: Diet, lifestyle, pads, loperamide, fibre supplements etc.

Figure 4: Algorithm of care for FI: Level II



1. E.g. rectal prolapse, cloaca, rectovaginal fistula
2. Prolapse surgery, reconstruction, fistula repair
3. Conservative or surgery

1.9.1 Specific treatments

Prior to these initial management strategies however, each patient should have the following excluded, and these will not all be considered here:

- Lower GI malignancy
- Acute disc prolapse/cauda equina syndrome
- Prolapsing 3rd degree haemorrhoids
- Acute anal sphincter injury secondary to obstetric injury (see below)
- Rectal prolapse

Further, the initial assessment of patients with FI includes the exclusion of faecal loading and potentially treatable causes of diarrhoea (e.g. infective, inflammatory bowel disease, irritable bowel syndrome) (Figure 3).

1.9.1.1 Management of obstetric injury

Guidelines updated by the Royal College of Obstetricians and Gynaecologists in March 2007, recommend that all women who sustain a 3rd or 4th degree perineal tear during childbirth should undergo timely repair of this injury in theatre, under regional or general anaesthesia, by a practitioner with formal training in anal sphincter repair techniques[170]. The guidelines advise that either an overlapping or end-to-end method of repair is acceptable for the external anal sphincter[170], however subsequent Cochrane review has suggested that at one-year follow up immediate primary overlapping repair is associated with lower risk of developing faecal urgency and anal incontinence, compared to end-to-end repair; however at 36 months there was no difference in flatus or faecal incontinence between the two techniques[171]. Both sources however acknowledge the paucity of high quality studies in this area.

Functional outcome following primary repair is often unsatisfactory, with up to 40% of women developing anal incontinence despite surgery [122, 172]. Long-term outcome after sphincter injuries is largely unknown [98].

1.9.2 Generalised treatments

1.9.2.1 Level I conservative therapies

Level I conservative strategies to treat FI aim to address all factors which may be involved in order to achieve satisfactory bowel emptying at a predictable time. They can be administered together or sequentially, and used appropriately, tailored to each patient's individual needs.

1.9.2.1.1 Education and 'lifestyle' interventions

In light of the well-documented association between FI and obesity, weight reduction may well be helpful in improving symptoms. Weight reduction was shown in one study to improve FI in obese women[173]. Another study reported a significant decrease in FI from 19.4% pre-operatively to 8.6% 1 year post-operatively in 101 women who underwent laparoscopic Roux-en-Y gastric bypass for morbid obesity[174]. Physical exercise may also be helpful in reducing symptoms, indeed one study of nursing home residents found exercise, in combination with increased fluid intake and regular toilet visits, significantly improved FI[175]. Reduction or, where possible, cessation of medications which adversely affect bowel function, either by causing diarrhoea or constipation, should be attempted. In addition to these measures, improvement of toilet facilities and patients' access to, for example, disabled toilet facilities, may well help with FI and the anxiety it is often accompanied by. There is also some evidence from a RCT that education and advice improves symptoms of FI, indeed this intervention was as effective alone as additional biofeedback or exercises in this study [176].

1.9.2.1.2 Diet and fluid intake

Common sense supports increasing fluid intake to ameliorate symptoms of constipation and the FI which may accompany this, especially in nursing home residents, however no data exist to support this recommendation. Diet modification is often recommended, in the form of increasing dietary fibre to improve stool consistency in those suffering incontinence associated with loose stool. A small placebo-controlled RCT of 39 patients found dietary fibre successfully reduced rate of FI in these patients[177].

1.9.2.1.3 Bowel management and retraining programmes

Education regarding the importance of establishing a regular and predictable pattern of bowel evacuation is important, as well as encouraging bowel emptying after a meal to utilise the gastrocolic reflex. There is, however, no evidence to evaluate or prove the effectiveness of this[169]. Encouraging the adoption of a sitting or squatting position to improve defaecation and teaching people techniques to facilitate bowel evacuation including stressing the importance of avoiding straining are also useful[168].

1.9.2.1.4 Medications

Alongside the use of medications to help prevent FI, it is also important to recognise and attempt to find alternatives where medications which contribute to FI are being used e.g. laxatives. For the pharmacological management of FI, a recent Cochrane review summarised 3 approaches: anti-diarrhoeal medications to improve stool consistency, medications to enhance sphincter function, and osmotic laxatives to improve stool consistency where FI is related to constipation in elderly patients[178]. Antidiarrhoeal medications (namely Loperamide, Diphenoxylate plus atropine, and Codeine) were shown to improve symptoms in patients with liquid stool, however, this evidence was limited. Loperamide was associated with more side effects than placebo,

although dose titration is possible to reduce side effects whilst improving continence[178]. Loperamide has also been shown to improve continence by directly increasing anal sphincter tone[179]. Medications that enhance anal sphincter tone were also found to reduce FI however evidence was again limited e.g. Phenylephrine gel. Laxative use in elderly patients with constipation-associated FI again reduced faecal soiling and the need for help from nurses. All trials, although randomised and placebo controlled, included only a small number of patients and had a short duration of follow-up[178].

1.9.2.2 Level II conservative therapies: Biofeedback and anal sphincter exercises/pelvic floor muscle training

Biofeedback involves the use of equipment to record or amplify body activities in order that these can be observed by the patient, using the principle of operant conditioning [180, 181] to improve function[168]. Many methods have been used to treat people with FI, though the three main modalities described involve rectal sensitivity training, anal sphincter strength training, recto-anal co-ordination training or a combination of the three[181]. Pelvic floor muscle training or anal sphincter exercises involve 'enhancing the strength, speed or endurance of voluntary anal sphincter contraction'[181]. Different treatment regimens again exist, and there is no consensus for the best method to treat FI. A recent Cochrane review analysed 21 randomised studies involving a total of 1, 525 patients, however these studies were often small and had methodological weaknesses[182]. The review recommend that it was not possible to definitively assess the role of anal sphincter exercises and biofeedback therapy in the management of FI, although there was some evidence to suggest that biofeedback and electrical stimulation may enhance the outcome of treatment compared to electrical stimulation alone or exercises alone. Exercises seem less effective than an implanted sacral nerve stimulator. There is some suggestion that some elements of biofeedback and sphincter

exercises may have a therapeutic effect, this is not certain, and larger well-designed trials are required to confirm or refute this[181].

1.9.2.3 Surgical interventions

In patients in whom the above conservative strategies have failed to satisfactorily resolve symptoms of FI, a specialist surgical opinion can be sought.

1.9.2.3.1 Sphincter repair

NICE recommends all patients with a full thickness external anal sphincter defect of ≥ 90 degrees should be considered for a sphincter repair[168]. This operation is usually performed on patients who have suffered anal obstetric injury[182]. Various techniques are described, however, the most commonly performed procedure is an anterior overlapping sphincteroplasty[183]. Whilst good results are achieved in the short term (3 months), a summary of numerous retrospective studies reports long-term continence rates ranging from 15% to 60%[183]. A review of sphincteroplasty and SNS revealed that sphincteroplasty remains a good option for the management of incontinence due to sphincter defect, despite new technologies[184].

1.9.2.3.2 Sphincter augmentation

In patients with major sphincter disruption or after failure of other intervention, e.g. SNS, a patient can be considered for a neosphincter, for which the two options are a stimulated graciloplasty or an artificial anal sphincter. The level of evidence for both procedures is low (small observational case series) and they are both associated with a high incidence of morbidity[185]. They should only be performed in specialised centres and patients should be given a realistic picture of the outcomes[168]. No randomised controlled trial data exist for either procedure[186].

An artificial anal sphincter is placed around the native sphincter via perianal tunnels. It remains inflated with fluid until the patient wishes to defecate, at which time it is

deflated by a manual pump implanted into the scrotum of men or labia majora of women. Like most treatments for FI it was first developed for the treatment of urinary incontinence[187]. Careful patient selection for this procedure is required since a successful outcome requires the ability to operate it. Case series report successful treatment in 49-83% of patients[183].

Gracilis neosphincter or dynamic graciloplasty has largely been replaced by sacral nerve stimulation and the artificial bowel sphincter for the treatment of FI with apparently better functional outcomes and quality of life[185, 188, 189]. It involves transposition of the gracilis muscle to function as a neosphincter, with the addition of electrical stimulation to maintain tonic contraction. Success rates are reported as 60-75% for dynamic graciloplasty in one series[183], however third party prospective evaluation reported less favourable results, however still concluding that this technique deserves consideration in patients who have failed other conventional treatments [190].

All data on gracilis neosphincter (GN) and artificial anal sphincter (AAS) are however very poor (mostly case series), with variable methods of data collection and differing outcome criteria. High incidence of morbidity in the long term are reported for both with infection rate AAS vs. GN 21.7% vs. 35.1%, revision rate AAS vs. GN 37.5% vs. 40.6% and AAS explantation rate of 30%[185].

1.9.2.3.3 Antegrade continence enema

This procedure was first described in 1990[191] and is mostly used in the paediatric population. It may however be considered in selected adults with faecal soiling secondary to constipation and poor colonic motility[183]. It involves creating an access point for irrigation in the right large bowel (most commonly the appendix), and irrigating it, as necessary, with an electrolyte or bowel cleansing solution. Functional results are good, with about 75% adults achieving continence with the procedure[192-194].

1.9.2.3.4 Radiofrequency energy and injectable materials

The delivery of radiofrequency energy to the internal anal sphincter (the SECCA procedure), is thought to improve continence by restructuring of collagen, leading to a more robust internal anal sphincter. It is proposed for patients with mild-moderate faecal incontinence refractory to conservative management, who are unable or unwilling to undergo surgical treatment. Series include between 8 and 50 patients, with most showing a significant improvement in incontinence scores after treatment[183]. Long-term outcomes seem variable with one study reporting most patients still having treatment success at 5 years[195] whilst another reported only 22% patients having treatment success at a mean of 40 months[196]. Adverse events reported from this procedure are minor (infection, minor bleeding, haematoma, anal pain)[98].

Injections of various materials into the sphincter complex in order to add bulk and treat FI have been trialed. The procedure involves low associated morbidity[183]. Ideal candidates are those with faecal seepage or mild to moderate faecal incontinence who have failed conservative management, but are not ready or willing to try more invasive surgical procedures. The procedure does not preclude future surgical treatments such as SNS or sphincter replacement. Various agents have been trialed and of the five randomised trials identified by the recent Cochrane review, most reported a short term benefit from injection regardless of the material used, including placebo saline injection[197]. However, no long-term data were available and the quality of most studies was poor. One pivotal randomised study of dextranomer in stabilised hyaluronic acid (NASHA Dx), based on 206 patients, found it to be significantly better than sham at 6 months based on 50% FI episode reduction, with a 52% response rate in the active vs. 31% response rate in the sham arm, yielding a NNT of 4.4 [198]. Treatment did not significantly improve FI quality of life; data for complete continence and effects on anorectal physiology or imaging were not provided. Hence, the magnitude of benefit,

mechanisms of action and factors that predict response to therapy merit further study.[199] Sustained long-term benefit (up to 3 years) has also been reported recently.[200]

1.9.2.3.5 Stoma

Creation of a colostomy or ileostomy provides definitive control of FI. It should be considered when FI severely restricts quality of life, but only once all appropriate non-surgical and surgical options, including those at specialist centres, have been offered. Such patients should be referred to a stoma care service. Interestingly, quality of life for patients with a colostomy for faecal incontinence was shown in one study to be higher than that of patients with faecal incontinence[201], whilst another study found patients with stomas generally reporting a high level of satisfaction with over 80% saying they would likely or definitely choose to undergo the procedure again[202].

1.9.2.3.6 Neuromodulation

1.9.2.3.6.1 Sacral Nerve Stimulation

NICE advise that a trial of temporary SNS should be considered for people with FI in whom sphincter surgery is deemed inappropriate. Those patients may have an intact anal sphincter or a disruption. In those with a defect, contraindications to repair may include atrophy, denervation, a small defect, absence of voluntary contraction, fragmentation of the sphincter or a poor quality muscle (NICE). All patients should be informed of the risks vs. benefits and undergo a trial stimulation of at least 2 weeks. Patients should be offered SNS on the basis of their response to PNE, and this should be performed at a specialist centre that has experience of performing this procedure.

SNS is a form of neuromodulation (i.e. a technology which impacts on neural interfaces to produce benefit), which employs chronic, low-voltage electrical stimulation to recruit residual function of pelvic organs by direct or indirect stimulation of the sacral spinal nerves. It is growing in popularity due to its minimally invasive technique,

avoiding possibly hazardous surgery to the bowel or anal sphincter, well cited success rates, minimal morbidity (reported as 5-26%) and no reported mortality[203]. A recent systematic review identified 61 studies of sacral nerve stimulation where the median success rates were 63% in the short term, 58% in the medium term and 54% in the long-term[203]. Quality of life scores also improved in the short and long term following SNS[203]. Furthermore another study reported women who have undergone SNS for FI have also benefitted from improvements in urinary, sexual and vaginal symptoms and also a global benefit of pelvic floor health[204]. Age, gender, aetiology of FI and physiology results do not impact efficacy of SNS[205]. Also, SNS does seem effective in patients with sphincter defects, and the success of SNS does not seem to be correlated with degree of sphincter defect i.e. sphincter defect is not a contraindication to SNS[206, 207]. However, nearly all studies with SNS have been uncontrolled. Thus, despite the widespread popularity of SNS and abundant case series data,[208] there has still been no high quality randomised trial of efficacy or effectiveness. The only cross-over study to include more than 2 patients[209] enrolled 34 patients of whom only 27 participated in the crossover with significant issues of performance and attrition bias (5 patients were excluded due to lack of efficacy or to adverse events). In this study the number of episodes of FI declined by 90% during stimulation versus 76% without stimulation.[209] Economic evaluation of SNS has been carried out, and its incremental cost effectiveness ratio of £25 070 per QALY gained falls well within the NICE £30 000 per QALY recommended threshold[210].

1.9.2.3.6.2 Tibial Nerve Stimulation

The benefits of SNS over other surgical techniques to treat FI are evident, since SNS has reduced the need for potentially hazardous surgery to the anus itself, whilst producing seemingly favourable outcome data[203]. SNS however, is not successful in all patients, and there are others for whom this option is not available (due to comorbidities,

patient choice or local expertise). SNS also requires two operations that, despite advances in technology and technique, may still lead to complications[210]. Although it is cost effective compared to other surgical options[211], SNS does have high equipment costs (approx. £10,000 pp) and costs associated with on-going management[212].

In the last ten years, another neuromodulatory technique has been developed; Tibial Nerve Stimulation (TNS). Its concept is that, via electrical stimulation of the tibial nerve, similar changes in anorectal neuromuscular function can be achieved as with SNS, but without the need for a permanent surgically implanted device along with the attendant risks. It was first described in 1983 by McGuire et al. in patients with urinary incontinence using a transcutaneous electrode over the tibial nerve, producing data suggesting long term effectiveness[213]. The method was adjusted by Stoller in 1999, through the use of a percutaneous needle with a ground electrode on the ipsilateral extremity[214]. In 2003, Shafik proposed using PTNS for FI and achieved a reported 78% functional success in 32 patients[215].

Two main delivery methods of TNS are described:

Percutaneous tibial nerve stimulation (PTNS); involving electrical stimulation via a needle placed adjacent to the tibial nerve just above the ankle. This is now most commonly delivered via the Urgent® PC neuromodulation system (Uroplasty Ltd., Minnetonka, MN, USA). Treatment is typically delivered as twelve 30-minute treatments, given usually weekly for 12 weeks or sometimes twice weekly for 6 weeks.

Transcutaneous Tibial Nerve Stimulation (TTNS); electrical stimulation is delivered via two pad electrodes placed over the tibial nerve just above the ankle. This is usually delivered via a TENS machine (Transcutaneous Electrical Nerve Stimulation). Treatment regimens vary considerably though administration is usually in 20-30

minute sessions over a period of weeks or months. I have no knowledge of this method being used outside of the research setting in the UK.

1.9.2.3.6.2.1 Physiological effects of tibial nerve stimulation

The possible mechanism of action of TNS in the treatment of FI is not well studied. Since TNS was borne from the hypothesis that its shared nerve roots (L1-S3) could result in similar effects to the bladder and anorectum (innervated from S2-S4) achieved by SNS, there is a presumed similarity to the mechanism of action of the two neuromodulatory modalities[216].

SNS and TNS act on the nervous system, but what is unknown is whether the effect is mediated by central or peripheral effects, which may be somatic (sensory or motor) or autonomic, or a combination of the aforementioned. Investigation of the effects of neuromodulation could be carried out either by analysing changes invoked by electrical stimulation of a nerve itself, or assessing end organ changes. Due to complexities and difficulties of examining the former[217] most studies have concentrated on end organ effects. Given the therapeutic use, we would anticipate that end organ effects of TNS and SNS would be within the GI tract, and most likely within the colon, rectum and/or anus.

Studies of SNS attest to alteration in rectal sensation, up-regulating the striated muscle function of the external sphincter, and reduction in detrimental spontaneous anal relaxations and rectal contractions[215, 218-223]. Data reporting end organ effects following TNS are far fewer, however some studies of clinical effectiveness do report changes in anorectal physiology tests, most commonly anorectal manometry[215, 218, 224-230]. Most of these studies were non-randomised case series; one showed no change in anorectal manometry[229], whilst others showed improvements in maximum squeeze pressure[218, 225, 227, 230] or an improvement in both maximum resting and maximum squeeze

pressure[226, 228]. Two of these studies were randomised, and included sham treatment arms. It is interesting to note that, although both showed an improvement in anal manometric function following treatment in the active treatment arms, these responses were also seen in the sham treatment arms, with no significant differences between the groups[225, 230].

Experimental studies of PTNS have mainly concentrated on the afferent mediated effects. A study of the effect of electrical stimulation over the tibial nerve in the rat demonstrated an increase in the peak amplitude of primary cortical evoked potentials by 45.1%, findings homologous to those with acute S1 nerve stimulation [231]. This was supported by a clinical study for the treatment of overactive bladder where treatment was associated with an increase in long latency somatosensory evoked potentials, whereas placebo was not[232]. A further study suggested that PTNS inhibited bladder activity by depolarising somatic sacral and lumbar afferent fibres[233].

A recent review article into the clinical and experimental literature regarding mechanism of action of SNS[234] reported that data pertaining to the effects of SNS on anorectal and colonic function are extremely heterogeneous, and no constant change has been demonstrated. There were also discrepancies between clinical and experimental data. Data quality was poor, with most studies comprising case series or cohort studies in humans, making them subject to considerable selection and performance bias. Six studies used a randomised, double-blind design, the data from which, Carrington *et al.* have assimilated[234]. There was strong human evidence (in the form of a RCT) to support the theory of colonic motor effects, and strong animal evidence to support the theory of central nervous system effects. There was some evidence in human studies (RCT data) to support the theory of rectal sensory effects and central nervous system effects (cohort study data). There was also some evidence from animal studies to support the theory of colonic motor effects. Conclusions of this

study indicated the likely influence of SNS on anorectal function occurs at a pelvic afferent or central level.

Studies into the mechanism of action of TNS are extremely limited, and those into SNS do not draw reproducible conclusions. This area is limited somewhat by a lack of tools to measure therapeutic effects, for example, whilst attempting to measure effects of SNS on gastrointestinal sensation may be straightforward on the anus or rectum, this poses more of a problem in the upper GI tract or colon, which are inaccessible. Similarly, the measurements of effect in the peripheral nervous system are more straightforward than the inaccessible central nervous system.

1.9.2.3.6.2.2 Clinical effects of tibial nerve stimulation.

These will be considered in Chapter 3.

2 Aims and objectives

2.1 Knowledge gap

Neuromodulation is an emerging field in the treatment of FI. It is advantageous in its relative ease of application, limited morbidity, low associated cost and apparent relative efficacy. SNS is now commonplace, however it is not available everywhere and is associated with significant treatment costs, often necessitating regional funding requisition on a case-by-case basis.

TNS is a newer, cheaper and less invasive treatment, which is thought to work on a similar pathway, and seems to have similar efficacy. A recent RCT of TTNS vs. sham shows no clinical benefit of the active treatment. Whilst there are numerous case reports indicating clinical efficacy of PTNS, including one small RCT comparing PTNS to TTNS to sham, where PTNS appears superior, no sham-controlled trial has been performed. A well-conducted and adequately powered randomised sham-controlled trial is required to definitively answer the question regarding efficacy of PTNS to treat FI.

2.2 Objectives

The aim of this thesis was to definitively investigate the effect of PTNS in the treatment of faecal incontinence, with the following specific objectives:

1. To perform a systematic review of the current evidence base for tibial nerve stimulation to treat faecal incontinence (Chapter 3);
2. To assess the short term clinical efficacy of PTNS compared to sham electrical stimulation in the treatment of patients with significant faecal incontinence in the CONFIDeNT Study, a large multicentre randomised sham controlled trial (Chapter 4);

3. To identify factors predictive of successful PTNS from the CONFIDeNT Study data (Chapter 5);
4. To follow-up all patients enrolled in the CONFIDeNT Study to assess medium-term outcomes (Chapter 6).

3 Clinical effects of tibial nerve stimulation: A systematic review

3.1 Aims

The aim of this review was to provide a comprehensive and systematic overview of PTNS and TTNS in the treatment of FI. The two methods of TNS, described in Chapter 1 (1.8.2.3.6.2) above will be addressed separately. This chapter represents an update of a systematic review published in the British Journal of Surgery in 2014[235].

3.2 Methods

A published systematic review[235], using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework[236] to minimise risk of bias, has been updated to include more recently published trials. The protocol developed for review, detailing pre-specified methods of the analysis and eligibility for the review, was adhered to. The following criteria were used.

3.2.1 Inclusion criteria

Studies of any design, including case series, case–control and randomised controlled trial (RCT) designs, reporting TNS for FI from January 2003 to November 2014 were eligible for inclusion. The study must have provided data for at least ten patients treated with PTNS or TTNS. Only studies that clearly reported at least one of the selected review outcome measures (baseline and post-intervention) and a clear follow-up period were eligible for inclusion. No exclusions were placed on study centre or patients, in terms of age, sex, ethnicity or aetiology of FI. All eligible studies required a definitive intervention by PTNS or TTNS for FI; reports of PTNS or TTNS for primarily urinary symptoms, or mixed symptoms, were excluded.

3.2.2 Outcomes

The pre-specified primary outcome was the success rate of therapy, based on a 50% or greater decrease in the number of weekly FI episodes. Secondary outcomes were: reduction in weekly FI episodes; cure rates of the treatment (100% reduction in episodes); improvement in the Cleveland Clinic Incontinence Score (CCIS) or similar (including St Mark's Continence Score)[160]; improvements in quality of life (QoL) measures (generic and condition-specific); and improvements in any other outcomes reported by individual studies.

3.2.3 Methods for quality appraisal

Critical appraisal of the studies was considered by study type and data collected and potential sources of bias were considered. Case series, which comprised most of the PTNS and TTNS studies, were assessed using the National Institute for Health and Care Excellence (NICE) 'Quality Assessment for Case Series' system[40], which assesses characteristics of methodology, outcomes and interpretation from a possible score of 8. The randomised trials were evaluated using the Jadad score[237], which awards points for randomisation method, blinding and account of all patients. The score is out of a possible 5 points, with a score of above 3 indicating good quality. The RCTs were also evaluated using the Cochrane Collaboration tool for assessing risk of bias in randomised trials[238], which evaluates six specific domains and reports on whether there is a high, low or unclear risk of bias in each area.

3.2.4 Search

A comprehensive re-search of the literature was carried out on 3rd November 2014, to update that carried out for a previously published review on 10 February 2013[235] using PubMed, MEDLINE, Embase and Evidence-Based Medicine reviews (including the Cochrane database of systematic reviews and the Cochrane central register of

controlled trials). Search terms used were 'tibial nerve stimulation faecal incontinence' ("tibial nerve"[MeSH Terms] OR ("tibial"[All Fields] AND "nerve"[All Fields]) OR "tibial nerve"[All Fields]) AND stimulation [All Fields] AND ("faecal incontinence"[All Fields] OR "fecal incontinence"[MeSH Terms] OR ("fecal"[All Fields] AND "incontinence"[All Fields]) OR "fecal incontinence"[All Fields]). Full-text copies of all studies deemed to be potentially relevant were obtained and assessed for inclusion. Where papers cited other potentially important references, these were also assessed. Systematic reviews, RCTs and case series of patients with FI who had undergone TNS were searched for relevant data sets. There was no blinding as to the names of studies, authors, institutions or publications. Search results were cross-referenced with bibliographies of relevant papers.

3.2.5 Study selection

Eligibility assessment was performed in an un-blinded but standardised manner. Methodological quality of included studies was assessed independently using the PRISMA assessment criteria [236]. Exact duplicate data sets generated from the same cohort of patients were excluded where possible, or highlighted where this was uncertain.

3.2.6 Summary measures and analysis

Formal data synthesis was not possible owing to heterogeneity between study designs and outcome measures. Summary measures for individual outcome variables across broadly homogeneous studies were limited to descriptions of percentages, medians and ranges.

3.3 Results

The re-search revealed seven further studies which met the inclusion criteria, giving a total of 20 studies. Studies were published between 2003 and 2014, and included 10 case series of PTNS [215, 218, 224, 226-228, 239-242], a comparative case matched study of PTNS vs. SNS [243], a prospective clinical audit of SNS and PTNS[244] , five case series of TTNS[229, 245-248] , a randomised controlled trial of TTNS vs. sham[230] , a randomised study of PTNS vs. TTNS vs. sham[225] , and a randomised study comparing daily with weekly TTNS[249]. A total of 773 patients (range 10-146) underwent active treatment for FI of various aetiologies, with 565 undergoing PTNS (this does include 2 publications from one institution and 4 publications from a second institution where likely duplication of patient data has occurred) and 208 undergoing TTNS (two of these studies are again from one institution). Results are presented as those from randomised studies, those from PTNS studies (including the PTNS arm of a randomised studies), and those from TTNS studies (including the TTNS arms of randomised studies).

3.3.1 Quality of studies

3.3.1.1 Randomised studies

Using the Jadad score [237], two RCTs scored 4, and the other scored 3 out of a possible 5 marks, indicating good quality (Table 6). Appraisal of RCTs using the Cochrane Collaboration tool for assessing risk of bias (Table 7) identified two area of potential bias, in the forms of incomplete outcome data and the risk of performance bias as patients were self-treating at home, in the larger RCT comparing TTNS with sham stimulation[230]. In the smaller RCT comparing PTNS *versus* TTNS *versus* sham[225], two areas of potential bias were identified (blinding and conduct of sham). In the final RCT comparing two treatment protocols for TTNS[249], four areas of potential bias were identified: The trial was only single blinded; analysis was not on intention to treat

basis, since one patient was excluded as outcome data were not available; patients self-treated at home with no consideration for performance bias; and no comparison between the two groups were made (all analysis was per group compared to baseline).

Table 6: Critical appraisal of randomised controlled trials using Jadad Score

Study	**Randomisation**	**Blinding**	**Account of all patients**	**Score**
Leroi *et al.* *(*2012)	2	1	1	4
George *et al.* *(*2013)	2	1	1	4
Thomas *et al.* *(*2013)	2	0	1	3

Table 7: Critical appraisal of randomised controlled trials using the Cochrane Collaboration tool for assessing risk of bias in randomised studies.

Domain	Description	Judgement of risk of bias
Leroi *et al*. (2012)		
Sequence generation	Random number table stratified based on CCIS score	Low
Allocation concealment	Random number table stratified based on CCIS score – unclear whether allocation central, web-based or other	Unclear
Blinding of participants, personnel and outcome assessors	Double-blinded – patient and evaluating physician blinded to treatment	Low
Incomplete outcome data	13 patients dropped out and therefore not analysed	High
Select outcome reporting	All outcomes reported	Low
Other sources of bias	Performance bias – patients treated at home	High
George *et al*. (2013)		
Sequence generation	Sealed-envelope randomisation	Low
Allocation concealment	Sealed, windowless envelopes used	Low
Blinding of participants, personnel and outcome assessors	Single-blinded – patient blinded only	High
Incomplete outcome data	No missing outcome data	Low
Select outcome reporting	All outcomes reported	Low
Other sources of bias	Paper reported that sham arm was suitable only for comparison with TTNS arm, and not for PTNS arm	High
Thomas *et al. (*2013)		
Sequence generation	Sealed-envelope randomisation	Low
Allocation concealment	Sealed, opaque envelopes used	Low
Blinding of participants, personnel and outcome assessors	Single blinded – assessor only	High
Incomplete outcome data	Outcome data missing for one patient who was excluded	High
Select outcome reporting	All outcomes reported	Low
Other sources of bias	No comparison between groups made Performance bias – patients treated at home	High

CCIS, Cleveland Clinic Incontinence Score; TTNS, transcutaneous tibial nerve stimulation; PTNS, percutaneous tibial nerve stimulation.

3.3.1.2 Non-randomized studies

Critical appraisal of the case series, using the NICE quality assessment form, is shown in Table 8. All studies scored between 3 and 6 out of 8. The median score for TTNS studies was 5 (range 3–6) and that for PTNS studies was 4 (3–5).

Table 8: Critical appraisal of case series using the National Institute for Health and Care Excellence Quality Assessment for Case Series form.

Reference	Score
PTNS series	
Shafik *et al.* (2003)	3
De la Portilla *et al.* (2009)	4
Govaert *et al.* (2010)	5
Boyle *et al.* (2010)	4
Findlay *et al.* (2010)	4
Hotouras *et al.* (2012)	5
Arroyo *et al.* (2014)	4
Al Asari *et al.* (2014)	5
Hotouras *et al.* (2014)	4
De la Portilla *et al.* (2014)	5
Hotouras *et al.* (2014)	4
Lopez Delgado *et al.* (2014)	3
Median (range)	4 (3-5)
TTNS series	
Queralto *et al.* (2006)	3
Vitton *et al.* (2009)	4
Vitton *et al.* (2010)	6
Eleouet *et al.* (2010)	5
Thomas et al. (2013)	6
Median (range)	5 (3-6)

3.3.2 Results of randomised studies

The three randomised studies of PTNS and TTNS included a large multicentre RCT of TTNS vs. sham containing 144 patients,[230] a smaller single-centre study of PTNS vs. TTNS vs. sham containing 30 patients[225], and a further small single-centre study comparing twice weekly vs. daily TTNS. The outcomes of these RCTs are summarised in

Table 9, with further details of secondary outcomes and treatment protocols in Appendix 1 (Table 39 and Table 40).

Table 9: Faecal incontinence episodes and Cleveland Clinic Incontinence Score outcomes in trials of percutaneous and transcutaneous tibial nerve stimulation

Reference	*n**	Initial treatment period in months ‡	Follow-up (months from start of treatment)	FI episodes/week				CCIS			
				Median (range)§	*P*	≥ 50% reduction (%)	100% continence (%)	Improvement in CCIS (% of patients)	≥ 50% improvement in CCIS (% of patients)	Median CCIS§	*P*
Leroi *et al.*											
TTNS	73 (68)	3 (180)	3	1.7 (0–23) to 1.0 (0–14.3) (−0.7)#	0.004	0	0	n.r.	47¶	11 to 8 (−3)	< 0.001**
Sham	71 (63)	3 (180)	3	2.9 (0–25) to 1.6 (0–23.6) (−1.3)#	0.06	0	0	n.r.	27¶	11 to 9 (−2)	< 0.001**
George *et al.*											
PTNS	11 (n.r.)	1.5 (12)	1.5	8.2(5.2) to 1.8(0.8) (−6.4)†#	n.r.	82***	82	–	–	–	–
TTNS	11 (n.r.)	1.5 (12)	1.5	7.4(5.9) to 5.1(4.2) (−2.3)†#	n.r.	45***	45	–	–	–	–
Sham	8 (n.r.)	1.5 (12)	1.5	6.5(3.5) to 4.7(3.5) (−1.8)†#	n.r.	13***	13	–	–	–	–
Thomas *et al.*											
TTNS (Daily)	14 (14)	1.5 (42)	1.5	5 (11.1) to 3.5 (4.3) (-1.5)	0.025	n.r.+	21	-	-	-	-
TTNS (Weekly)	15 (12)	1.5 (12)	1.5	6.5 (5) to 3 (6.5) (-3.5)	0.31	n.r.+	0	-	-	-	-

*Values in parentheses are numbers of women. †Data reported as mean(s.d.). ‡Number of initial treatments shown in parentheses; there were no top-up treatments in either study. §From baseline to start of treatment; difference is shown in parentheses. ¶More than 30 per cent improvement in Wexner score. FI, faecal incontinence; CCIS, Cleveland Clinic Incontinence Score; TTNS, transcutaneous tibial nerve stimulation; n.r., outcome measured but not reported; n.s., not significant; PTNS, percutaneous tibial nerve stimulation. #Leroi *et al.*[36], no significant difference between groups; George *et al.*[37], $P = 0.042$ (PTNS *versus* TTNS and sham, ANCOVA test) Thomas *et al*. significance between groups not reported. **Leroi *et al.*[36], no significant difference between groups. *** statistically significant across all groups. + reported as 'about half' in each group.

3.3.2.1 Primary outcome

In the TTNS vs. sham study[230], no patient in either group had a 50% or greater reduction in weekly FI episodes. In the PTNS vs. TTNS vs. sham study[225], 82% of patients in the PTNS group, 45% of patients in the TTNS group and 13% of those in the sham group had treatment success based on this outcome. This was statistically significant across all groups: there were significantly more patients with treatment success in the PTNS group than in the TTNS group, and in the TTNS group compared with the sham group ($p = 0.035$) (Table 9). In the TTNS study[249] it is commented that 'about half' of the patients in each group achieve this outcome, though no further detail is given.

3.3.2.2 Secondary clinical outcomes

In the TTNS vs. sham study[230], there was a significant reduction in median number of weekly FI episodes, from 1.7 (range 0–23) to 1 (0–14.3) in the TTNS group ($p = 0.004$), and in median CCIS in both TTNS (from 11 to 8) and sham (from 11 to 9) groups ($p < 0.001$) (Table 9). However, there were no significant differences between the two groups. In the three-arm study[225], there was a reduction in the mean number of FI episodes in the PTNS group (from 8.2 to 1.8), in the TTNS group (from 7.4 to 5.1) and in the sham group (from 6.5 to 4.7). However, significance within the groups was not reported. Statistical analysis demonstrated a significantly greater reduction in the PTNS group ($p = 0.042$). CCIS was not collected in the three-arm study. In the TTNS study[249], there was a statistically significant reduction in the median number of weekly FI episodes from 5 (SD 11.1) to 3.5 (SD 4.3) ($p=0.025$) in the daily TTNS group, however there was no significant reduction in the twice weekly TTNS group. CCIS was not collected in this study.

3.3.2.3 Quality of life

In the TTNS vs. sham study[230], both TTNS and sham groups had significantly improved scores in all four Faecal Incontinence Quality of Life Scale (FIQL) domains compared with baseline, but there were no significant between-group effects. In the three-arm study[225], all groups demonstrated improvement in the FIQL and Short Form 36 (SF-36®; QualityMetric, Lincoln, Rhode Island, USA) scores; however, there were few statistically significant differences between groups. In the TTNS study[249] there was no improvement in any domain of the FIQL or SF-36® scores in the twice weekly group, however, there was a significant improvement in the lifestyle and embarrassment domains of the FIQL and in the physical functioning domain of the SF-36® score in the daily TTNS group. No comparisons between groups were made. (Table 39 Appendix 1).

3.3.3 Results of studies of percutaneous tibial nerve stimulation

PTNS studies included ten case series [218, 224, 226-228, 239, 240, 250, 251] (one study[215] included a 'control' group for comparison), one comparative case matched study of PTNS vs. SNS [243], one prospective clinical audit of SNS and PTNS [244] and one small single-centre randomised single-blind trial (PTNS vs. TTNS vs. sham)[225], comprising a total of 565 patients who received active treatment. All studies treated patients in 12 or 14 30-min sessions, with nine studies performing weekly treatments for 12 weeks [218, 224, 226, 228, 240-242, 244], three studies [225, 239, 243] performing twice-weekly treatments for 6 weeks and one study performing treatment every other day for 4 weeks [215]. The median length of follow-up was 5 (range 1.5–29) months from start of treatment, indicating that three studies [225, 241, 242] followed up patients only immediately after treatment had ended. Nine studies [215, 218, 224, 226-228, 239, 242, 243] then offered 'top-up' treatments to those who perceived treatment benefit (range 3–72 top-ups). Outcomes of patients receiving PTNS are summarised in Table 10, with further secondary outcomes and details of treatment protocols shown in Appendix 1 (Table 41 and Table 42).

Table 10: Faecal incontinence episodes and Cleveland Clinic Incontinence Score outcomes in studies of percutaneous tibial nerve stimulation.

Reference	*n*	No. of initial weekly treatments in weeks	No. of top-ups	Follow-up (months from start of treatment)	FI episodes/week				CCIS			
					Median (range)†	*P*	≥ 50% reduction (%)	100% continence (%)	Improvement in CCIS (% of patients)	≥ 50% improvement in CCIS (% of patients)	Median CCIS†	*P*
Shafik *et al.*‡	32 (32)	14 (4)	8	22*	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	–	
De la Portilla *et al.*	16 (11)	12 (12)	8	3	n.r.	n.r.	n.r.	n.r.	81	38	13 to 9 (−4)*	< 0.001
				8					63	44	13 to 8 (−5)*	0.001
				14					63	31	13 to 9 (−4)*	0.001
Govaert *et al.*	22 (16)	12 (6)	> 72	1.5	7 to 3 (−4)	0.082	63	n.r.	n.r.	n.r.	12 to 8 (−4)*	< 0.001
				12	7 to 1 (−6)	0.029	59				12 to 6 (−6)*	0.001
Boyle *et al.*	31 (30)	12 (12)	3	5	4 to 0 (−4)	< 0.001	71	39	65	n.r.	13 to 7 (−6)	< 0.001
Findlay *et al.*	13 (13)	12 (12)	0	4	n.r.	n.r.	n.r.	n.r.	–	–	–	
Hotouras *et al.*	88 (88)	12 (12)	0	3	5 to 1 (−4)	< 0.001	n.r.	n.r.	n.r.	n.r.	12 to 9 (−3)	< 0.001
George *et al.*	11 (?)	12 (6)	0	1.5	8 to 2 (−6)*	n.r.	82	82	–	–	–	
Arroyo et al.**	16 (15)	12 (12)	12	3	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	-
				6	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	10 to 5 (-5)	0.006
Al Asari *et al.*^^^	21 (21)	12 (6)	>3+	6	-	-	-	-	n.r.	47	15 to 8 (-7)*	< 0.001
				12					n.r.	31	15 to 9 (-6)*	< 0.001
Hotouras *et al.*^	146 (128)	12 (12)	0	3	4 to 1 (-3)	n.r.	n.r	n.r	n.r	n.r	12 to 10 (-2)*	n.r.

De la Portilla *et al.*	30 (21)	12 (12)	12	3	-	-	-	-	80	43	14 to 10 (-4)*	<0.005
				8					77	40	14 to 7 (-7)*	<0.005
				14					77	37	14 to 9 (-5)*	<0.005
				27					77	43	14 to 9 (-5)*	<0.001
Hotouras *et al.*	115 (103)	12 (12)	***	3	5 to 1 (-4)	<0.001	n.r.	n.r.	n.r.	n.r.	12 to 9 (-3)	<0.001
				29^^	5 to 1 (-4)	<0.001	52				12 to 10 (-2)	<0.001
Lopez-Delgado *et al.*	24 (19)	12 (12)	6	3	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	15 to 14 (-1)	0.389
				6							15 to 10 (-5)	0.018
Summary (median (range))	565 (497)	12 (12-14)	6 (0->72)	6 (1.5-29)	5 (4-8) to 1 (0-3) (-4)		63 (52-82)	61 (39-82)	77 (63-81)	40 (31-47)	13 (10-15) to 9 (5-14)	

All values have been calculated to the nearest integer. *Mean values. †From baseline to end of treatment; difference is shown in parentheses. ‡Outcome data reported in groups only. ⁺Once per week for 3 weeks, once every 15 days followed by once every 3-4 weeks and then 5-6 weeks as required. ^this study contains 88 patients from the previously reported study in this institution. **All patients had sphincter defect of 90-180^0. ^^^ Comparative case-matched study of PTNS vs SNS. ^^ median value. *** 3 weaning sessions plus median 2 (range 1-27). FI, faecal incontinence; CCIS, Cleveland Clinic Incontinence Score; n.r., outcome measured but not reported; n.s., not significant.

3.3.3.1 Primary outcome of PTNS

Four studies[224, 225, 239, 242] reported a 50% or greater reduction in the number of FI episodes immediately after treatment, in 52–82% of patients. In the single study[239] that reported on this outcome after 1 year, 59% of patients still experienced treatment success (Table 10).

3.3.3.2 Secondary clinical outcomes of PTNS

Two studies [224, 225] reported rates of 'complete continence' following treatment of 39% and 82%. Statistically significant reductions in median weekly FI episodes were reported in four studies[224, 239, 241, 242]. These reductions were between 4 and 6 episodes per week (Table 10).

The CCIS was used as an outcome measure in all but two studies [225, 240], with five[224, 226, 228, 241, 242] reporting a significant reduction in the median CCIS and five [218, 227, 239, 242, 243] in the mean score (all $P \leq 0.006$) (Table 10).

3.3.3.3 Quality of life outcomes of PTNS

Eight studies [218, 225, 227, 228, 239, 240, 242, 243] reported changes in quality of life after treatment, with some reaching statistical significance, especially in the domains of depression, coping/behaviour, embarrassment and lifestyle. Different methods were used to collect these data. Other outcome measures are also shown in Appendix 1 (Table 41).

3.3.4 Studies of transcutaneous tibial nerve stimulation

TTNS studies included five non-randomised case series [230, 245-248] and three RCTs (one of TTNS vs. sham[230] a second of PTNS vs. TTNS vs. sham[225] and the third to compare two treatment protocols of TTNS[249]), comprising a total of 208 patients who received

the active treatment. All studies used different treatment protocols, with a median treatment duration of 1.5 (range 1–3) months involving a median of 42 (12–180) treatments. All studies, apart from one[248], used unilateral stimulation. Follow-up was for a median of 3 (1.5–15) months. Two studies[229, 245] offered top-up treatments to patients who had perceived benefit from treatment. Outcomes of patients receiving TTNS are summarised in Table 11 with further secondary outcome data and details of treatment protocols in Appendix 1 (Table 43 and Table 44).

Table 11: Faecal incontinence episodes and Cleveland Clinic Incontinence Score outcomes in studies of TTNS

Reference	*n**	Initial treatment period in months ‡	Length of top-up treatment (months)	Follow-up (months from start treatment)	FI episodes/week				CCIS			
					Median (red)§	*P*	≥ 50% reduction (%)	100% continence (%)	Improvement in CCIS (% of patients)	≥50% improvement in CCIS (% pts)	Median CCIS§	*P*
Queralto *et al*.	10 (10)	1 (20)	2	1	–	–	–	–	80	60	13 to 3 (−10)	n.r.
				4					80	70	13 to 1.5 (−11.5)	n.r.
Vitton *et al*.**	12 (9)	3 (90)	Nil	3	–	–	–	–	33	8	13.5 to 13 (−0.5)	n.s.
Vitton *et al*.	24 (22)	3 (90)	Nil#	3	–	–	–	–	42	4	14 to 12 (−2)	0.025
				15†					29	8	12 to 10 (−2)	n.r.
Eleouet *et al*.	32 (30)	1 (56)	Nil	1	–	–	–	–	††	16	14.5 to 11 (−3.5)†	< 0.001
				3								
				6								
Leroi *et al*.	73 (68)	3 (180)	Nil	3	1.7 to 1.0 (−0.7)	0.004	0	0	n.r.	47¶	11 to 8 (−3)	< 0.001
George *et al*.	11 (n.r.)	1.5 (12)	Nil	1.5	7.4 to 5.1 (−2.3)†	n.r.	45	45	–	–	–	–
Thomas *et al.*	14 (14)	1.5 (42)	Nil	1.5	5 to 3.5 (-1.5) †	0.025	n.r.+	21	–	–	–	–
Thomas *et al.*	15 (12)	1.5 (12)	Nil	1.5	6.5 to 3 (-3.5)	0.31	n.r.+	0	–	–	–	–
Thomas *et al.*	17 (15)	1.5 (42)	Nil	1.5	6 to 2 (-4)	0.029	59	12	–	–	–	–
Summary (range)	208	1.5 (1-3)	Nil	3 (1.5–15)	(−0.7 to −4)		45 (0–59)	12 (0–45)	42 (29–80)	16 (4–70)	(−0.5 to −11.5	

*(women) †Mean values. ‡(Number of initial treatments). §From baseline to end of treatment; (difference). ¶ >30% improvement in CCIS. #Therapy continued at home. **Patients with stable inflammatory bowel disease. ††Mean score improved. FI, faecal incontinence; CCIS, Cleveland Clinic Incontinence Score; n.r., not reported; n.s., not significant, + 'about half' in each group.

3.3.4.1 Primary outcome of TTNS

Three studies[225, 230, 248] reported on the primary outcome; immediately after treatment 0% of patients in the first study, 45% in the second and 50% in the third had a greater than 50% reduction in the number of weekly FI episodes (Table 11). A further study[249] commented that 'about half' of patients achieved this outcome.

3.3.4.2 Secondary clinical outcomes of TTNS

Complete continence following treatment was reported by four studies[225, 230, 248, 249] with a median of 12% (range 0-45) experiencing complete continence immediately after treatment. A significant reduction in the median number of weekly FI episodes was reported in two studies[230, 248], from 1.7 to 1 ($P = 0.004$) in the first, and 6 to 2 (p=0.03) in the second. The mean reduction in weekly FI episodes in another study[225] reporting this outcome was 2.3 (from 7.4 to 5.1), although this study did not report significance, the final study reporting this outcome[249] found a significant reduction in the mean weekly FI episodes in the group having daily treatment (-1.5 episodes (5 to 3.5), p=0.025), but no significant reduction in the group having twice weekly treatment. The CCIS was used as an outcome measure in five studies[229, 230, 245-247]; the median reduction in CCIS ranged from -0.5 to -11 immediately after treatment and was reported as significant in three studies[230, 245, 247] (Table 11).

3.3.4.3 Quality of life outcomes of TTNS

Seven studies[225, 230, 245-249] reported quality of life data before and after TTNS treatment, although different outcome measures were used. All studies showed significant improvement in some quality of life domains immediately after treatment. This effect tended to reduce over time. Other outcome measures are also shown in Appendix 1 (Table 43).

3.4 Summary of the evidence

The current TNS literature contains mostly non-randomised observational studies of PTNS and TTNS. In terms of high quality evidence, there is only one large RCT[230] and this compares TTNS with sham.

3.4.1 Evidence for PTNS

There is no high quality evidence for PTNS in the treatment of FI. From this review, the success rate of PTNS in the treatment of FI is in the region of 52–82%, for the primary outcome measure chosen (patients achieving at least a 50% reduction in weekly FI episodes).

3.4.2 Evidence for TTNS

There is an adequately powered and well conducted trial in the literature indicating that TTNS is not superior to sham electrical stimulation in the treatment of faecal incontinence[230]. Using the chosen primary outcome measure, no patients in either arm of the trial achieved treatment success.

3.4.3 Discussion of the evidence

It is clear that the evidence surrounding PTNS in the treatment of FI is limited, and current studies are inadequate to draw conclusions about the effectiveness of PTNS compared with sham. This systematic review highlights the ongoing problems concerning trials of therapies for faecal incontinence.

There is a lack of standardised and universally accepted outcome measures. Moreover, this problem includes not only what outcome measure is chosen, but also the way in which this measure is presented and interpreted. Most studies used the CCIS or bowel diary data (or both) as their primary outcome. The presentation and interpretation of

bowel diary data has made comparison between studies difficult. Many of the included studies compared the group mean or median number of pre-treatment and post-treatment FIE to assess for significant improvement. Weekly FIE, as a count, has an over-dispersed Poisson distribution i.e. greater variability than expected. Therefore attempting to define a clinically significant mean reduction in FIE per week in a population of patients with widely dispersed starting FI frequencies is very difficult. Therefore, although a significant result has been demonstrated in these studies, this does not necessarily correlate with a clinically significant result. Other studies have chosen to counter this problem by adopting a categorical measure of percentage reductions i.e. the proportion of patients who have a ≥50% reduction in FIE per week, which is likely to be a much more realistic indication of success, but was unfortunately not universally reported. It is also important to remember that bowel diary data has only been collected for a short (usually 2-week) period at the beginning and end of treatment, and just because a patient scores 'zero' on a bowel diary this does not necessarily signify their incontinence is cured (a point ignored in some studies where terms such as 'complete continence' are used to describe this occurrence).

CCIS have been compared by testing for statistical differences between the mean or median pre-treatment and post-treatment scores. Analysis in this way gives no indication of individual patient experiences i.e. percentage that has experienced improvement or deterioration, or the magnitude of individual improvement. Since this outcome denotes a score, it also indicates nothing about how many are actually 'better' or 'cured'. A better way to interpret this data may be to indicate the proportion of patients with a certain or significant improvement (e.g. improved by 25%, 50%, 75% or 100%), which some studies have done, but again this was not universal.

Studies were generally hampered by a lack of common treatment indication, protocol denoting treatment timing and duration, and follow-up period. Whilst some studies

reported patients had failed conservative treatment strategies, others did not. Similarly in those which required patients to have failed conservative treatment, those treatments were not discussed or standardised. Treatment protocols for PTNS were fairly standardised. All used one of two sets of equipment discussed above; the number of treatments was fairly constant throughout studies and was always performed once or twice weekly. The presence, frequency and duration of top-ups however were different across all studies. No conclusions can therefore be drawn regarding which treatment protocol is most efficacious. For TTNS therapy, whilst similar equipment was used in all studies, each treatment protocol differed significantly in terms of the number of treatments, frequency and duration, as well as top-up treatment protocols. TTNS patients had up to 180 treatments, which is obviously a factor of 10 greater than most PTNS treatment protocols included in this systematic review.

One potential advantage of TTNS over PTNS is the simplicity of treatment administration, resulting in the possibility of patient-administered home treatments; indeed, some studies of TTNS discussed here involved patient-administered home treatments. This impacts upon the potential patient acceptance of the treatment along with the associated costs, which again have to be borne in mind when comparing the two. No study evaluated costs or cost effectiveness.

4 The CONFIDeNT Study

4.1 Introduction

There are serious limitations, as noted in Chapter 2, regarding the current published evidence for PTNS in FI. No double blind placebo-controlled trial of PTNS in patients with FI has been performed, and this is important, as the effect of PTNS over and above that of attendance alone, is still unknown. Although PTNS is available in several centres in the UK, some are using it with speculation that it is little more than an expensive form of acupuncture.

4.1.1 Study Aims

The aim of this study was to assess the clinical effectiveness of PTNS compared to sham electrical stimulation, in the treatment of patients with significant faecal incontinence who have already failed conservative management strategies.

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

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

4.1.2 Hypothesis

A 12-week course of PTNS results in a clinical response rate of 55% compared to a sham response rate of 35%, with clinical response defined as the proportion of patients in whom the weekly number of faecal incontinence episodes is reduced by 50% or more.

4.2 Methods

4.2.1 Overview: Study design

The CONFIDeNT study was a UK based, multicentre, pragmatic, parallel arm, double-blind, randomised controlled trial comparing PTNS with sham electrical stimulation in the treatment of faecal incontinence. There was equal allocation to the two groups, with stratification by sex and centre. Outcomes were assessed following a standard 12-week treatment schedule.

4.3 Study outcomes

Clinical outcomes:

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

Primary outcome:

Responder vs. non-responder: Defined as a patient achieving ≥ 50% reduction in total FI episodes per week, as recorded on a 2-week self-completed bowel diary.

Secondary outcomes:

- Percentage change FI episodes per week (i.e. patients achieving ≥ 25%, ≥ 75% or 100% reduction in weekly FI episodes);
- Change in FI episodes per week as a continuous measure;
- Change in symptom severity score: St Mark's Continence Score (SMCS). A score from 0 (best) -24 (worst) with >5 indicating significant symptoms [252];
- Change in disease specific quality of life scores:

    - Gastrointestinal Quality of Life Index (GIQOL)[253]. A score from 0 (worse) to 180 (best); and
    - Faecal Incontinence quality of life scale (FIQOL) [161]. A score with 4 domains scored from 1 (worst) to 4 (best);
- Change in general quality of life measures: SF-36[254]. A score with 8 domains with scores given as percentages;
- Change in patients' health status and overall health using EQ-5D[255] questionnaire;
- Change in patient-centred outcomes questionnaire. A derivative of the ICIQ-B[256] questionnaire with a score from 1 (best) to 80 (worst);
- Likert scale of patients global impression of success (scale 0-10);
- Qualitative data:
    - Patient perceived impression of change in use of incontinence pads and constipating medications;
    - Patient perceived impression of change in urinary symptoms;
    - Patients' impression of the treatment in general;
    - Patients' perceived allocation (PTNS or sham);

Other outcomes recorded at each visit:

- Stimulation parameters
- Adverse events and concomitant medications

4.3.1 Clinical centres

Centres with specialist expertise in faecal incontinence, including nurse-led (or equivalent) continence services, were invited to participate in the study. Centres had to demonstrate experience with PTNS; having previously completed a full set of 12 treatments in a minimum of three patients. Each centre also required a minimum of 2 staff to run the trial and ensure satisfactory blinding.

4.3.2 Study population

All adult patients attending the specialist continence or pelvic floor clinics at each of the centres were considered for participation in the study. This included patients with FI symptoms sufficiently severe to warrant intervention, in whom medically supervised conservative therapies had failed (a combination of diet, pelvic floor exercises, biofeedback and anti-diarrhoeal medication). Specialist investigations including structural and functional anorectal assessment were not mandatory, and anal sphincter injury was not a contra-indication.

4.3.3 Inclusion criteria

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

4.3.4 Exclusion criteria

- Inability to provide informed consent for the research study
- Inability to fill in the detailed bowel diaries required for outcome assessments (including patients who do not speak / read English)
- Significant neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease (including any patient with painful peripheral neuropathy)
- Anatomical limitations that would prevent successful placement of needle electrode

- Other medical conditions precluding stimulation: e.g. bleeding disorders, certain cardiac pacemakers, peripheral vascular disease or ulcer, lower leg cellulitis
- Congenital anorectal anomalies or absence of native rectum due to surgery
- A cloacal defect
- External full thickness rectal prolapse
- Previous rectal surgery (rectopexy / resection) done < 12 months prior to the study (24 months for cancer)
- Stoma in situ
- Chronic bowel diseases such as inflammatory bowel disease leading to chronic uncontrolled diarrhoea
- Pregnancy or intention to become pregnant
- Previous experience of SNS or PTNS

4.3.5 Data collection

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

Visit 1: Interest - eligibility: At this appointment, eligibility was determined on the basis of defined inclusion and exclusion criteria, listed above. Eligible subjects were provided with adequate explanation of the aims, methods, anticipated benefits and risks of participating in the study and given a patient information sheet containing this information. Patients were allowed at least one week to consider their participation. Patients who remained interested were provided with a bowel diary to complete over 2 weeks, and counselled on how to fill this diary in. Appointments were then booked for Visits 2-14, with Visit 2 being at least 2 weeks later to allow time for diary completion.

Visit 2: Consent – confirm eligibility - baseline assessment – randomisation – first intervention: At this appointment consent was confirmed, and patients were reminded of the need to be logistically able to complete the full protocol of 12 sessions at weekly intervals. Urine pregnancy tests were performed to exclude pregnancy in all females of childbearing potential.

The researcher then recorded all baseline data of faecal incontinence history, past medical history and medication usage, and the patient completed the baseline questionnaires. They also handed in the completed bowel diary, which was checked for completeness. If the patient failed to complete the bowel diary properly, they were given another 2-week bowel diary to complete and returned 2 weeks later for the trial to commence. If they failed a second attempt, they were withdrawn. Another patient was recruited in their place.

The researcher then performed the randomisation, recorded this information, and (now unblinded) delivered the first 30-minute intervention (real PTNS or sham). Parameters of stimulation were recorded. A GP letter, informing the GP of the patient's involvement in the trial, was sent out.

Visit 3-13: intervention – interim information: At appointments 3-13, an unblinded researcher (who may have been same person as in Visit 2) delivered the 30 minute intervention, before first checking randomisation allocation. They enquired about adverse events, concomitant medication usage and pad usage, and recorded this information.

At Visit 7, patients were given a one-week interim bowel diary to fill in between Visits 7 and 8. This bowel diary was collected and checked at Visit 8.

At Visit 13, patients were given a two-week bowel diary to complete prior to attending Visit 14, two weeks later.

Visit 14: final study visit: The final study visit was performed by a blinded member of the research team (i.e. somebody who was not present at visits 2-13). At this appointment, the bowel diary was collected and checked for completeness. The patient was then asked to complete the questionnaire document and the post treatment questionnaire.

The researcher then ensured all documents were present and filled in correctly, and the patient was then unblinded as to their treatment allocation and further follow-up was arranged as necessary.

Patients who failed to complete the Interim Bowel Diary between Visits 7 and 8, attempted this again the following week, and this was recorded as a protocol deviation. Patients who failed to complete the Final Bowel Diary were again asked to complete this after Visit 14, and they returned for another final study visit 2 weeks later. This was also a protocol deviation.

After completion of trial: After Visit 14, patients who received 'sham' stimulation were offered PTNS on an open label basis. Patients who received real PTNS and who derived significant benefit were offered 'top-up' sessions as per local departmental protocols. Patients who received real PTNS who derived no significant benefit were offered further treatments on an 'open-label' basis, following local departmental protocols.

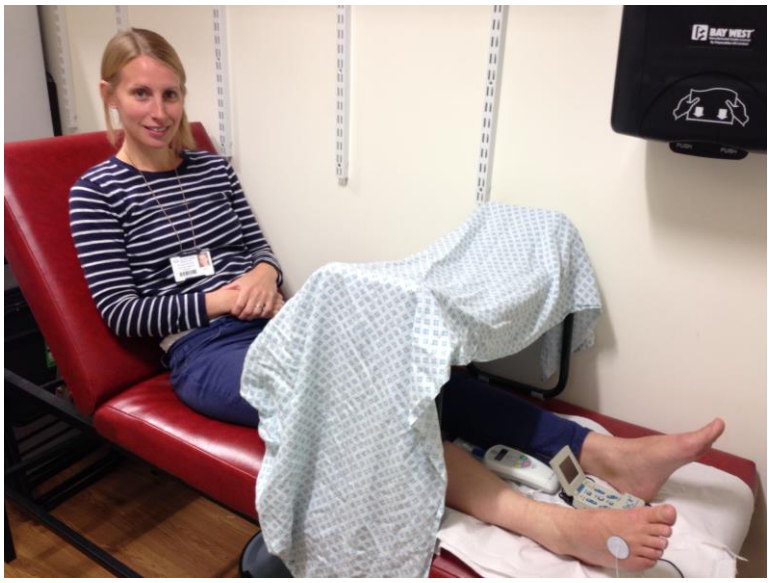
4.3.6 Study procedures: Delivery of PTNS and SHAM

PTNS was delivered via the Urgent® PC neuromodulation system (Uroplasty Ltd., Minnetonka, MN, USA) according to manufacturer's instruction. Sham electrical stimulation was delivered by transcutaneous electrical nerve stimulation (TENS) to the lateral forefoot (i.e. distant and contralateral to the tibial nerve) by modification of the validated sham technique used in the pivotal RCT of PTNS for overactive bladder.[257] Both groups used the recommended 12 weekly 30-minute outpatient stimulations.[235]

Treatments were tailored to patients' needs but protocol tolerance stipulated a minimum of ten treatments, with no two treatments less than five days or greater than ten days apart, to be completed in 13 weeks. Treatments given outside these windows were classified as a protocol deviation.

Treatments were given in individual treatment rooms, with patients lying, bare-legged, supine on a couch. All patients had identical equipment set-up, and this was hidden from patients' view using a stool covered with a sheet (Figure 5). Once the patient was comfortable but prior to equipment set-up, each researcher read a standardised paragraph to the patient, informing them of what to expect. This read "*I am now going to start the nerve stimulation treatment. I will be inserting a small electrode needle, like an acupuncture needle, into your leg and putting sticky electrodes onto your foot. When I turn the machine on you will be asked when you can first feel an electrical sensation in your ankle or foot. I will carry on increasing the intensity of this until it is slightly uncomfortable, then I will turn it down a little if necessary. Occasionally you may also feel numbness or slight movement of your toes. This is normal. I will set the machine up and leave it running for 30 minutes. You may or may not continue to feel the stimulation during this time – this is normal also. After 30 minutes have elapsed I will remove the needle and sticky electrodes (the machine automatically turns off at this time). If the treatment becomes uncomfortable at any point please let me know and I will turn it down or stop the machine*."

Figure 5: Photograph of equipment set-up



All patients then had an Urgent® PC machine and a TENS machine set up on their right foot, unless there was a reason why the right foot could not be used, under which circumstances the left foot was used (equipment set up can be seen in Figure 6). In the true PTNS arm, the Urgent ® PC was utilised as normal, and the TENS machine left turned off (Figure 6a). In the sham arm, the TENS machine was used to provide the electrical stimulation and the Urgent® PC was only turned on to provide the auditory stimulus (Figure 6b). Following satisfactory treatment commencement, the sheet was draped fully over the patient's feet, ensuring accidental unblinding could not take place. The researcher then filled in the paperwork for this visit and left the room, returning after 30 minutes to remove the equipment.

Treatment group: The site of needle insertion was identified and cleaned (5cm cephalad to and 2cm behind the medial malleolus). The needle was inserted, advanced 2cm, and connected to the lead wire, which in turn was connected to the stimulator. The calcaneal reference electrode was attached. The lead wire was then taped to the patient's leg (to mimic sham equipment set-up). The TENS machine was connected to two electrodes placed one under and one on top of the 5th toe but was not turned on.

The setting for PTNS therapy was determined by increasing the current whilst observing the patient's sensory response (appropriate response being in great toe or sole of foot) or motor response (plantar flexion of foot or great toe).

Figure 6: PTNS and sham equipment set up

(a) PTNS needle and calcaneal electrode. (b) TENS surface electrode placements

Sham group: the same protocol was followed as above, however the needle was inserted only 2mm into the skin. The lead was taped to the patient's leg near to the needle. Following equipment set up, the practitioner picked up the Urgent® PC machine and the TENS machine (Biostim M7 TENS unit, Biomedical Life Systems, Vista, California), and turned both machines on. The TENS machine was set to a pulse frequency of 10Hz and a pulse width of 200 microseconds. Then, pressing buttons simultaneously on both machines, the practitioner increased the current setting for TENS therapy by observing for any sensory or motor response in the toe or ankle. The TENS machine was used to provide the electrical stimulation and the Urgent® PC used only to provide the auditory stimulus.

This sham was shown in a departmental pilot to be both more acceptable and more realistic than that described by Peters *et al*, involving placement of a Streitberger needle. We also confirmed that this sham, using TENS to deliver the electrical

stimulation, does not stimulate the posterior tibial nerve (proven in a neurophysiological pilot by Consultant Neurophysiologist).

4.3.7 Treatment quality control

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

4.3.8 Withdrawal criteria

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

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

- Patient no longer wished to be involved in trial treatments
- Patient developed medical condition listed in exclusion criteria
- Patient became pregnant or intended to become pregnant
- Unblinding occurred
- Intercurrent illness

Withdrawn from the trial (no follow up data collected)

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

Early withdrawal was documented carefully and all patients were followed up in the NHS in the usual way. Permission was sought from each patient to use the data that had already been collected.

4.3.9 Randomisation

Patients were randomly assigned to receive either PTNS (active treatment) or sham electrical stimulation. Allocation was on an equal basis (1:1) with initial stratification by sex and then stratification of females by centre. Stratification by sex was used to reduce the potential confounding effects of variation in outcomes between male and female patients. Since males represent only 10% of patients and only 1 or 2 male patients were expected from each centre (due to differing pathophysiologies[6]), randomisation stratified on centre would increase the probability that all the males were allocated to PTNS or sham by chance. To avoid this situation, only females were stratified by centre, so achieving a near balance of PTNS and sham arms and allowing comparability by centre. Randomly permuted block sizes of randomly varying length (2, 4 and 6) were used to preserve allocation concealment. Allocation was managed with an automated, real-time, central web-based system, and performed by a local researcher following baseline data collection, immediately prior to delivery of first treatment.

For the duration of each patient's involvement in the trial (14 weeks) the patients and investigators performing clinical outcome assessments were masked to treatment allocation; investigators who delivered the treatment were not masked. After final data collection, patients were unmasked, and those in the sham group offered active treatment on an 'open-label' basis.

4.3.10 Blinding

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

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

Blinding of trial staff: At least two researchers were available at each site to run the study, one of whom performed the randomisation and all treatments and was necessarily unblinded, and the other remained blinded and carried out the final data collection.

4.3.11 Sample size calculation

Data published at the time of sample size calculation [218, 229, 239, 258] and our own data on 50 patients suggested a 60% success rate for PTNS based on our chosen primary outcome measure. There were no RCT data for PTNS in FI, however the pivotal level I

SumiT trial of PTNS in overactive bladder symptoms (OAB) [257] which used a similar global response assessment of urinary incontinence and intention to treat analysis observed a moderate or marked improvement in symptoms in 55% in the PTNS arm and only 21% in the sham arm. On the basis that placebo responses are frequently higher for bowel rather than bladder symptoms [259-261] we selected a sham response rate of 35% whilst keeping this more conservative estimate of treatment response of 55% (the difference of 20% we believe remains clinically important in relation to other therapies such as SNS). 212 patients were required to detect this difference with 80% power at the 5% significance level. We expected to screen 235 patients at baseline to allow for a 10% failure to attend for randomisation, baseline data collection and first treatment.

4.3.12 Statistical methods

All patients randomised were included in the intention-to-treat analysis. A statistical analysis plan was agreed prior to unmasking and analysis. Analysis was conducted using Stata version 12·1, interfacing with Realcom Impute for multiple imputation of missing outcome and baseline covariate data.[262] For all outcomes, mixed effects models were used, adjusting for outcome measured at baseline, sex and with a random effect for study centre.[263] Linear or logistic models were used, depending on the nature of the outcome, with results presented as effect sizes (odds ratios or differences in means) with 95% confidence intervals. Sensitivity analyses were performed (i) including only those patients who had ten treatment sessions within 13 weeks with no less than five and no greater than ten days between sessions (per protocol analysis), (ii) excluding any patients who had reported no episodes of FI in the baseline bowel diary, and (iii) excluding those centres who randomised less than five patients. Pre-planned subgroup analyses for the primary outcome were performed by sex, severity of FI (those with at

least seven weekly FIE vs. those with fewer than seven weekly FIE), age (<40, 40-60, >60 years) and type of FI (urge FI only vs. passive FI only vs. both).

4.3.13 Ethical arrangements and research governance

This trial was granted ethical approval in June 2010 (REC Reference: 10/H0703/25).

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

Information regarding study patients was kept confidential and managed by each study site in accordance with the Data Protection Act, NHS Caldicott Guardian Agreements, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

4.3.14 Trial oversight

The trial was under the auspices of the Chief Investigator and the Pragmatic Clinical Trials Unit (PCTU), Barts and The London School of Medicine and Dentistry. It was sponsored by Queen Mary University London and registered with the ISRCTN, registration number: 88559475. It was funded by the NIHR Health Technology Assessment programme (Ref: HTA 09/104/16).

The project was overseen by a Trial Steering Committee (TSC). The TSC comprised an independent chair, and met 6 monthly throughout to provide overall supervision and ensure the trial was conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice.

The Trial Management Group (TMG) was responsible for day-to-day project delivery in each participating centre. It met monthly and was answerable to the TSC.

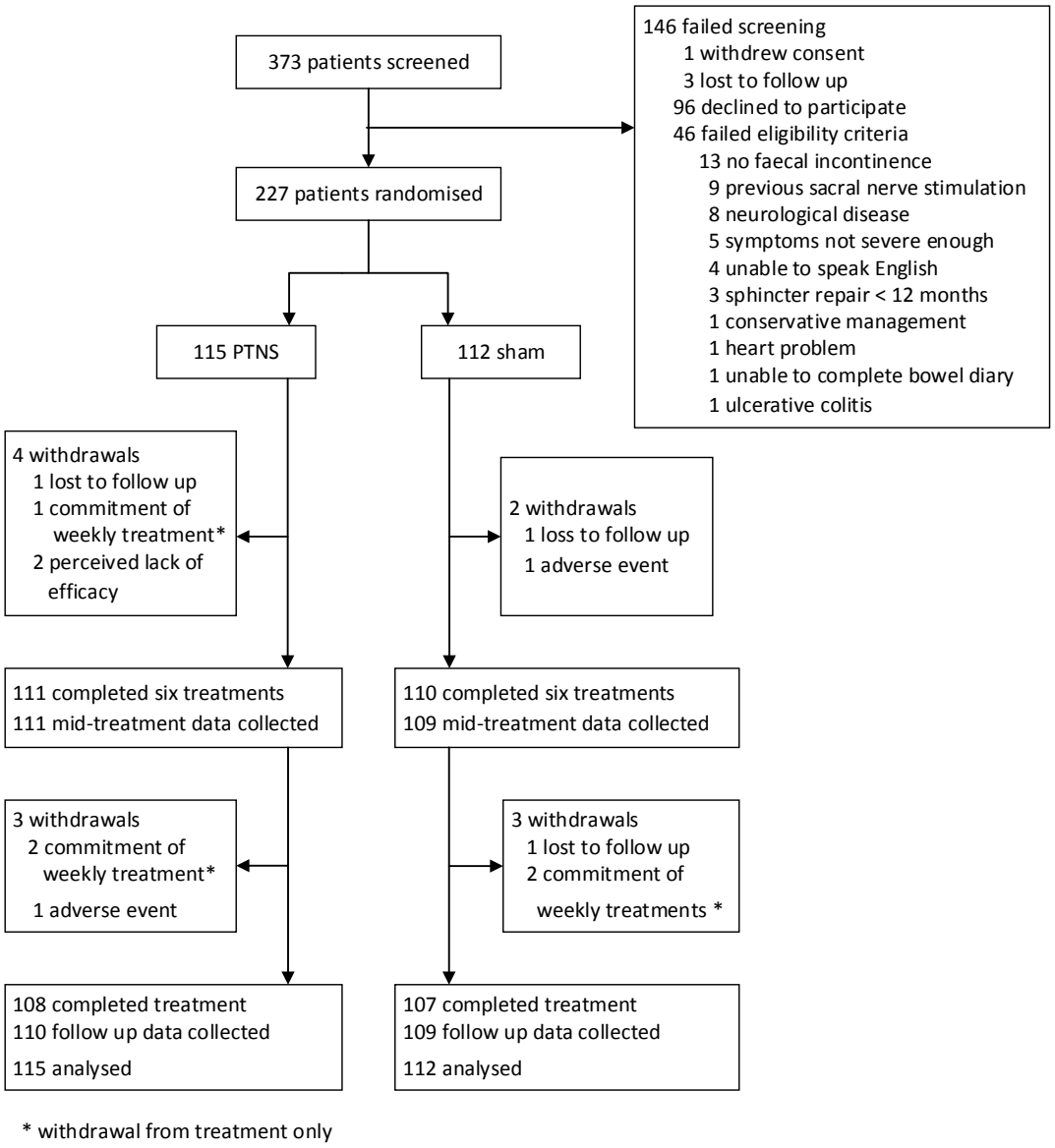
A data and safety monitoring committee (DSMC) was appointed to monitor unblinded comparative data and make recommendations to the TSC. The DSMC initially met together with the TSC, and subsequently two weeks prior to the TSC to enable any findings / recommendations to be submitted to the TSC. A DAMOCLES DSMC charter was adopted and an independent PCTU statistician provided the DSMC with an unblinded comprehensive report prior to each meeting.

4.4 Results

4.4.1 Patient flow

The CONSORT (Consolidated Standards of Reporting Trials) diagram, below, shows the flow of patients through the trial (Figure 7). Non-completing patients either withdrew from treatment (and remained in the trial), or withdrew from the trial, in which case no further data were collected from them. Permission was however sought to use the data which had already been collected.

Figure 7: Flow of patients through the study



4.4.2 Trial Recruitment

Seventeen of the 18 UK centres recruited patients for the trial between 23rd January 2012 and 31st October 2013 (Figure 8). The remaining centre was unable to participate due to staff shortages. Trial centres were: Barts Health NHS Trust, London; Aintree University Hospital, Liverpool; University Hospital Southampton NHS Foundation Trust; Sandwell General Hospital, Birmingham; Sheffield Teaching Hospital; Ching Way Medical Centre, London; Leicester Royal Infirmary; Queen's Medical Centre, Nottingham; Castle Hill Hospital, Hull; University College Hospital, London; Bristol

Royal Infirmary; St. Mark's Hospital, London; St Thomas' Hospital, London; Poole Hospital NHS Foundation Trust; Leeds General Infirmary; Pilgrim Hospital, Lincolnshire; University Hospital of South Manchester.

373 patients were screened and of these, 227 (61%) were randomised. The overall recruitment rate is shown in Figure 9. The number of patients per site ranged from 1-45. There were 12 patient withdrawals, 7 from the trial and 5 from treatment (Figure 7).

Figure 8: Recruitment of sites

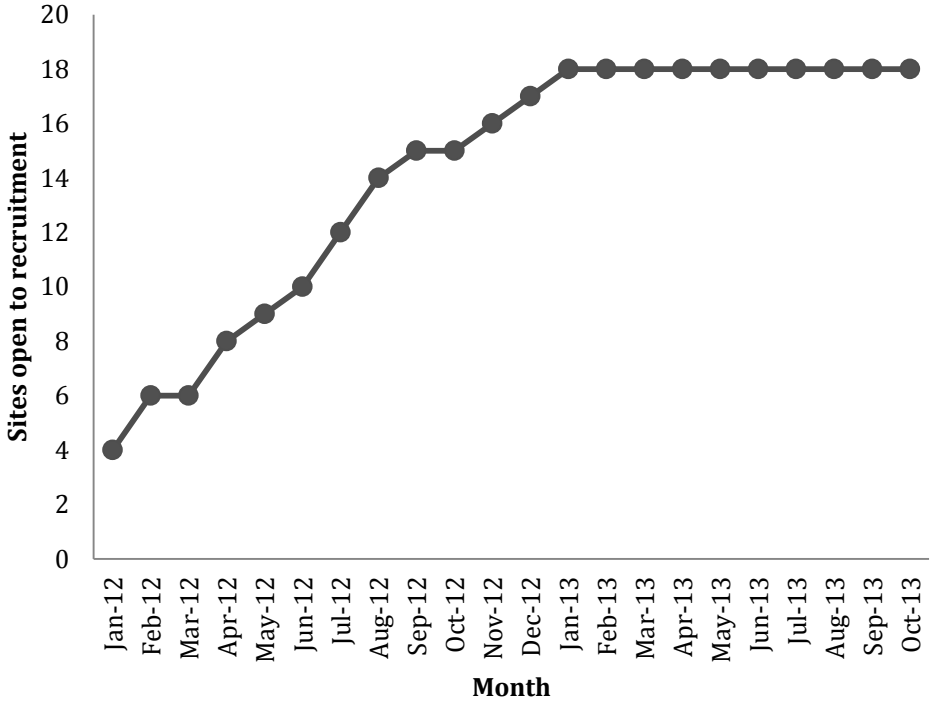
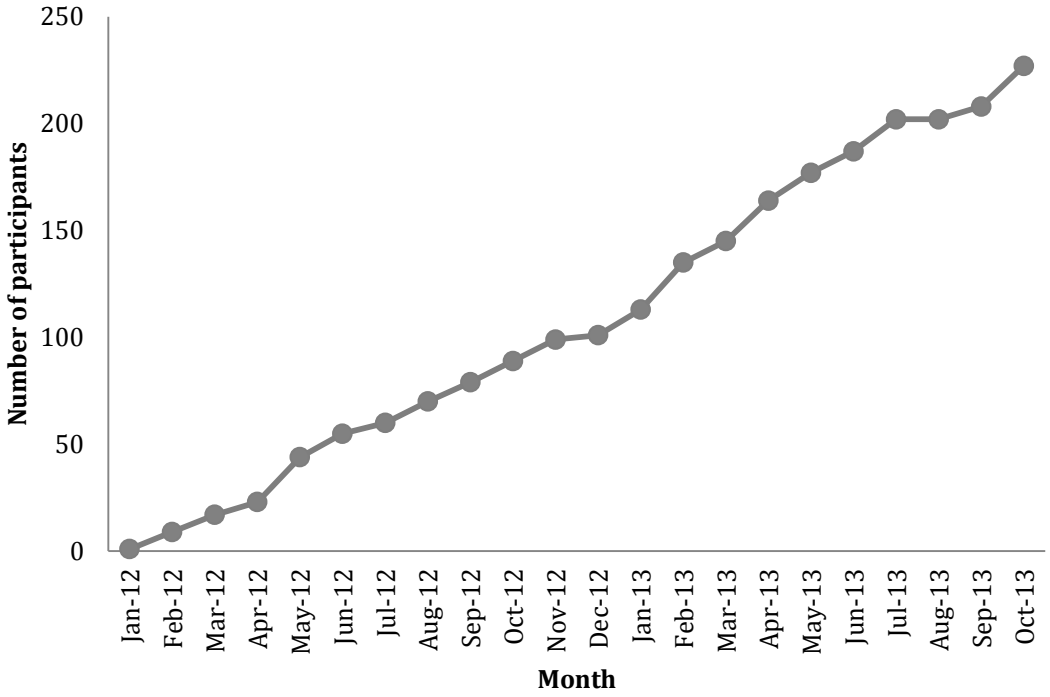


Figure 9: Patient recruitment



4.4.3 Data quality

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

4.4.4 Baseline data

227 patients were randomised; 115 to receive PTNS and 112 to receive sham electrical stimulation.

Baseline Findings

Ninety per cent of patients were female with mean age 57 years (range 20 to 85 years). Mean symptom duration was 8 years (range 5 months to 50 years). Baseline demographics and clinical data, previous treatments and relevant past medical history are summarised in Table 12. Demographics of the two arms were evenly matched for age and sex as per stratification. Of note approximately 40% of patients appear to have concomitant symptoms of FI and evacuatory difficulties (39% in PTNS arm and 44% in sham arm), and approximately 60% have concomitant urinary symptoms (61% in PTNS arm and 64% in sham arm).

Table 12: Baseline demographic and clinical data

	PTNS	Sham
Sex (female)	104 (90%)	101 (90%)
Age (years)	58 (50, 67)	58 (48, 65)
Duration of symptoms (months)	60 (24, 168)	48 (24, 108)
Obstetric history		
Parous*	95 (91%)	96 (95%)
Vaginal deliveries only*	90 (95%)	96 (100%)
C-Sections only*	5 (5%)	0 (0%)
Episiotomies or tears*	78 (87%)	82 (85%)
Bowel function history		
Passive FI	88 (77%)	86 (77%)
Urge FI	94 (82%)	93 (83%)
Flatus incontinence	74 (64%)	83 (74%)
Evacuatory difficulties	44 (39%)	49 (44%)
Straining	34 (30%)	37 (33%)
Digitation	12 (10%)	15 (13%)
Bladder function history		
Urinary symptoms	70 (61%)	72 (64%)
Urinary urgency	50 (43%)	49 (44%)
Urinary urge incontinence	39 (34%)	42 (38%)
Previous treatments for FI		
Anti-diarrhoeal medications	77 (67%)	67 (60%)
Biofeedback	56 (49%)	59 (53%)
Pelvic floor exercises	37 (32%)	36 (32%)
Fibre supplementation	18 (16%)	30 (27%)
Laxatives / suppositories / Irrigation	20 (17%)	16 (14%)
Anal sphincter repair	4 (3%)	4 (4%)
Other anal surgery	11 (10%)	8 (7%)
Defecatory advice	9 (8%)	7 (6%)
Other	5 (4%)	8 (7%)
Relevant medical history		
Hysterectomy*	30 (29%)	24 (24%)
Vaginal operation*	3 (3%)	2 (2%)
Pelvic operation *	19 (18%)	16 (16%)
Abdominal operation	28 (24%)	30 (27%)
Anal operation	6 (5%)	9 (8%)
Neck or back pain	15 (13%)	21 (19%)
Overactive bladder	15 (13%)	7 (6%)
Diverticular disease	4 (3%)	6 (5%)

Irritable bowel syndrome	1 (1%)	4 (4%)

Data are n (%) and median (interquartile range). *females only (% calculated from only females)

Bowel diary data at baseline

Baseline bowel diaries demonstrated a median of 6.0 FI episodes per week in PTNS patients, comprising a median of 3.0 urge faecal incontinent episodes and a median of 2.0 passive episodes. In the sham arm there was a median of 6.9 FI episodes per week, but with a slightly higher rate of passive FI (median 3.0 episodes) compared to urge episodes (median 2.5 episodes) (Table 13).

Table 13: Descriptive statistics of bowel diary data at baseline

	PTNS	**Sham**
Bowel diary data		
FI episodes/week *[median (interquartile range)]*	6·0 (2·0, 14·0)	6·9 (2·5, 16·0)
[mean (standard deviation)]	9·9 (11·2)	10·4 (10·9)
Urge FI episodes/week	3·0 (0·9, 8·0)	2·5 (0·5, 7·0)
	5·3 (7·2)	4·8 (5·9)
Passive FI episodes/week	2·0 (0·0, 7·5)	3·0 (0·0, 8·0)
	4·6 (6·0)	5·7 (7·6)

Data are median (interquartile range) and mean (standard deviation).

Other baseline outcome measures

Baseline St Mark's Continence Scores (SMCS) were similar between the arms, with a mean of 14.4 (standard deviation 3.7), in the PTNS arm and 15.4 (standard deviation 4.1) in the sham arm. All 211 patients who completed their SMCS had significant FI, on the basis of their score being greater than 5 (Table 14).

Table 14: Descriptive statistics of other outcome measures at baseline

	PTNS	**Sham**
St. Mark's Continence Score (0 [best]-24 [worst])		
	14·0 (12·0, 17·0)	16·0 (13·0, 18·0)
	14·4 (3·7)	15·4 (4·1)
St. Mark's Continence Score >5	110 (100%)	101 (100%)
Faecal incontinence quality of life scale scores		
Lifestyle (1[best] to 4 [worst])	2·7 (1·8, 3·4)	2·5 (1·7, 3·6)
	2·6 (0·9)	2·6 (1·0)
Coping and behaviour (1[best] to 4 [worst])	1·7 (1·2, 2·3)	1·6 (1·1, 2·6)
	1·9 (0·7)	1·9 (0·9)
Depression and self-perception (1[best] to 4·4 [worst])	3·1 (2·0, 3·4)	2·6 (2·0, 3·7)
	2·8 (0·9)	2·7 (0·9)
Embarrassment (1[best] to 4 [worst])	2·0 (1·7, 2·7)	2·0 (1·3, 2·7)
	2·2 (0·8)	2·1 (0·8)
Patient centred outcomes (1 [best] to 10 [worst])		
	8·9 (7·8, 9·8)	9·2 (8·3, 10·0)
	8·5 (1·6)	8·7 (1·7)
Gastrointestinal quality of life (36 [worst] to 180 [best])		
	130·0 (113·0, 41·0)	126·5 (109·0,39·0)
	126·7 (18·8)	123·8 (20·2)
SF-36 scores (%)		
Physical functioning	70·0 (45·0, 90·0)	65·0 (40·0, 85·0)
	65·7 (27·4)	61·4 (28·4)
Role-physical functioning	50·0 (0·0, 100·0)	25·0 (0·0, 75·0)
	46·4 (42·1)	36·4 (41·4)
Bodily pain	60·0 (40·0, 90·0)	57·5 (32·5, 90·0)
	61·3 (30·0)	58·2 (31·5)
General health	50·0 (35·0, 70·0)	50·0 (30·0, 70·0)
	51·2 (23·4)	50·3 (23·8)

Vitality	45·0 (30·0, 57·5)	50·0 (30·0, 60·0)
	43·9 (22·1)	42·7 (22·8)
Social functioning	62·5 (37·5, 75·0)	62·5 (37·5, 87·5)
	58·4 (28·8)	59·3 (31·6)
Role-emotional function	66·7 (0·0, 100·0)	33·3 (0·0, 100·0)
	58·4 (28·8)	59·3 (31·6)
Mental health	60·0 (44·0, 76·0)	64·0 (48·0, 76·0)
	60·3 (21·0)	60·8 (21·6)
EQ-5D index score (-0·594 [worst] to 1 [best])		
	0·73 (0·62, 0·85)	0·73 (0·62, 0·85)
	0·69 (0·27)	0·63 (0·34)

Data are n (%) , median (interquartile range) and mean (standard deviation).

4.4.5 Primary outcome

The proportion of patients achieving a ≥50% reduction in weekly FI episodes (FIE) was similar in both arms at 38% (39/103) for PTNS compared to 31% (32/102) for sham (unadjusted odds ratio 1.333; adjusted odds ratio 1.283, 95% CI 0.722-2.281, p=0.396) (Table 15 and Table 16).

Table 15: Results of intention to treat analysis (n=227)

Outcome	Odds ratio	95% confidence interval	p-value
Percentage reduction in weekly FIE			
≥ 50% (primary outcome)	**1.283**	**0.722, 2.281**	**0.396**
≥25%	1.264	0.730, 2.190	0.404
≥75%	1.615	0.770, 3.388	0.205
100%	1.635	0.592, 4.514	0.344
Outcome	**Difference in means**	**95% confidence interval**	**p-value**
Change in weekly FIE			
Total	-2.262	-4.185, -0.339	0.021
Urge	-1.456	-2.693, -0.219	0.021
Passive	-0.635	-1.668, 0.397	0.228
Faecal Incontinence Quality of Life			
Embarrassment	0.036	-0.151, 0.223	0.706
Coping	0.013	-0.171,0.197	0.889
Lifestyle	0.086	-0.075, 0.248	0.290
Depression	0.014	-0.297, 0.324	0.927
SF-36			
Physical functioning	-1.854	-6.992, 3.284	0.479
Role-physical	1.113	-8.866, 11.092	0.826
Bodily pain	-1.026	-6.815, 4.764	0.728
General health	-0.158	-4.749, 4.433	0.946
Vitality	-3.142	-8.129, 1.845	0.215
Social functioning	5.209	-0.740, 11.157	0.087
Role emotional	-4.815	14.802, 5.171	0.343
Mental health	-0.509	-4.831, 3.814	0.817
Other outcomes			
St. Mark's continence score	-0.047	-1.033, 0.939	0.925
Patient centred outcomes	-0.545	-1.081, -0.008	0.047
EQ-5D index score	-0.017	-0.078, 0.044	0.583
Gastrointestinal quality of life	-1.300	-5.168, 2.568	0.506
Likert scale of success	0.808	-0.055, 1.672	0.068

Table 16: Descriptive statistics for bowel diary outcomes at baseline and end of treatment

	Baseline		End of treatment	
	PTNS	**Sham**	**PTNS**	**Sham**
FI episodes/week	6.0 (2.0, 14.0)	6.9 (2.5, 16.0)	3.5 (1.0, 10.0)	4.8 (1.5, 12.8)
	9.9 (11.2)	10.4 (10.9)	6.4 (7.6)	9.1 (10.7)
UFI episodes/week	3.0 (0.9, 8.0)	2.5 (0.5, 7.0)	1.5 (0.0, 4.5)	1.5 (0.5, 5.5)
	5.3 (7.2)	4.8 (5.9)	3.0 (4.2)	4.4 (6.5)
PFI episodes/week	2.0 (0.0, 7.5)	3.0 (0.0, 8.0)	1.5 (0.0, 5.0)	1.5 (0.0, 6.5)
	4.6 (6.0)	5.7 (7.6)	3.4 (4.6)	4.7 (6.6)

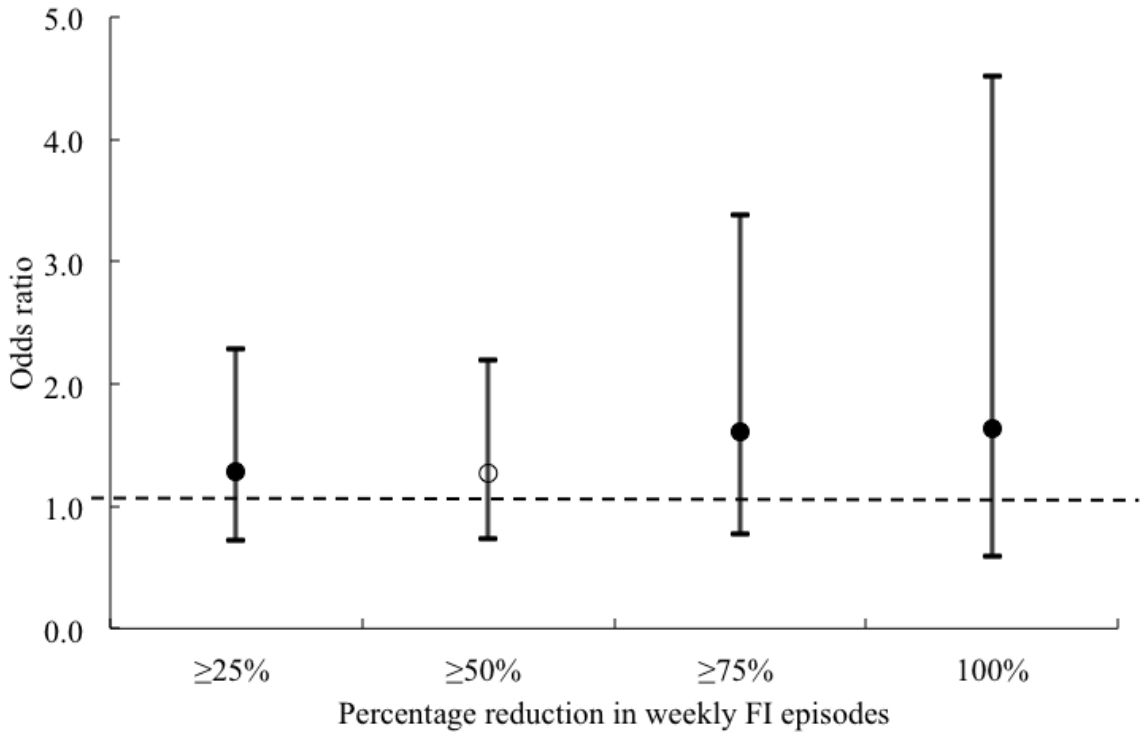
Data are median (interquartile range) and mean (standard deviation). UFI = Urge Faecal Incontinence; PFI = Passive Faecal Incontinence.

4.4.6 Secondary outcomes

4.4.6.1 Percentage change in FI episodes

No significant difference was observed between the PTNS and sham arms in the number of patients achieving ≥25%, ≥75% and 100% reduction in weekly FI episodes (Table 15 and Figure 10).

Figure 10: Categorical reductions in mean weekly FIE (adjusted odds ratios and 95% confidence intervals) for PTNS vs. sham group at 14 weeks.



4.4.6.2 Change in FI episodes as a continuous measure

There was a greater decrease in total weekly FI episodes in the PTNS compared to the sham arm (difference in means -2.3, 95% CI (-4.2 to -0.3) episodes per week, and this was significant (p=0.02). This comprised a reduction in urge FI episodes (-1.5, 95% CI (-2.7 to -0.2), p=0.02) but not passive FI episodes (-0.64, 95% CI (-1.67 to 0.40), p=0.23) per week (Table 15, Figure 11 and Figure 12). There was very little continued improvement from mid-treatment to end treatment (Figure 12), indicating that those who are likely to respond to treatment will have done this by week 6.

Figure 11: Adjusted difference in mean weekly FIE (95% CI) for PTNS vs. sham groups at 14 weeks.

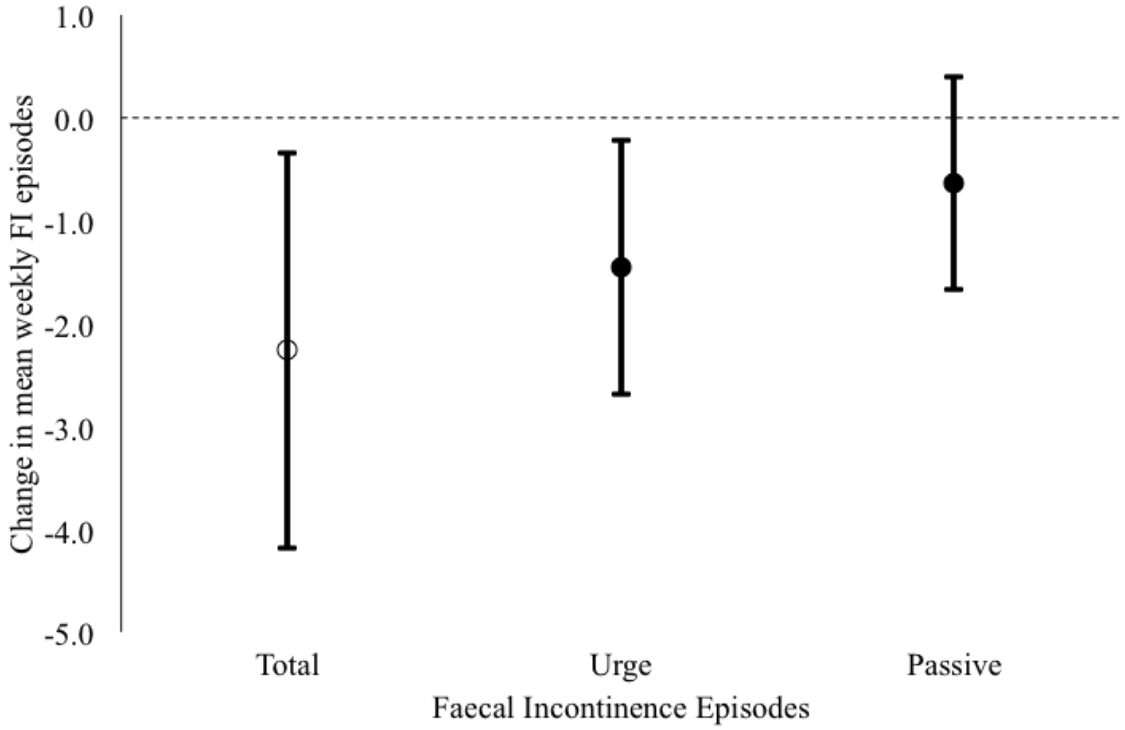
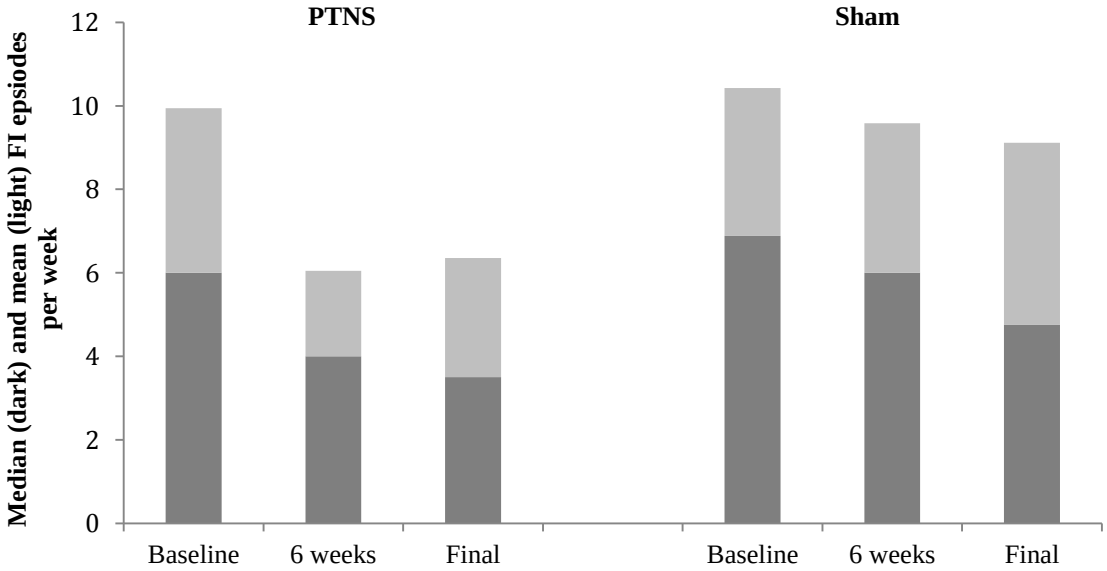


Figure 12: Frequency of FIE at baseline, after six treatments and at 14 weeks for PTNS vs. sham groups.



4.4.6.3 Change in symptom severity score: St Marks Continence Score

No significant difference in SMCS was observed between the PTNS and sham arms following treatment (difference in means -0.047, 95% CI (-1.033 to 0.939), p=0.93) (Table 15 and Table 17.

Table 17: Descriptive statistics for St. Mark's continence score at end of treatment.

	Baseline		End of treatment	
	PTNS	**Sham**	**PTNS**	**Sham**
SMCS	14.0 (12.0, 17.0)	16.0 (13.0, 18.0)	14.0 (11.0, 17.0)	15.0 (11.0, 18.0)
	14.4 (3.7)	15.4 (4.1)	13.9 (4.3)	14.6 (4.6)
SMCS >5	110 (100%)	101 (100%)	104 (100%)	101 (100%)

Data are n (%), median (interquartile range) and mean (standard deviation).

4.4.6.4 Change in Quality of Life Measures

No significant differences were seen in the disease specific (FIQOL and GIQOL) or generic (SF-36) quality of life measures between the PTNS and sham arms following treatment (Table 15, Table 18, Figure 13 and Figure 14).

Table 18: Descriptive statistics for quality of life outcomes at baseline and end of treatment

	Baseline		End of treatment	
	PTNS	**Sham**	**PTNS**	**Sham**
Faecal incontinence quality of life scale scores				
Lifestyle (1[best] to 4 [worst])	2.7 (1.8, 3.4)	2.5 (1.7, 3.6)	3.0 (2.2, 3.7)	2.9 (1.9, 3.7)
	2.6 (0.9)	2.6 (1.0)	2.8 (0.9)	2.8 (1.0)
Coping and behaviour (1[best] to 4 [worst])	1.7 (1.2, 2.3)	1.6 (1.1, 2.6)	1.9 (1.3, 2.6)	1.7 (1.2, 2.9)
	1.9 (0.7)	1.9 (0.9)	2.0 (0.8)	2.0 (1.0)
Depression and self-perception (1[best] to 4 [worst])	3.1 (2.0, 3.4)	2.6 (2.0, 3.7)	3.1 (2.2, 3.7)	2.6 (2.0, 3.9)
	2.8 (0.9)	2.7 (0.9)	2.9 (1.0)	2.8 (1.0)
Embarrassment (1[best] to 4.4 [worst])	2.0 (1.7, 2.7)	2.0 (1.3, 2.7)	2.7 (1.7, 3.0)	2.3 (1.7, 3.0)
	2.2 (0.8)	2.1 (0.8)	2.4 (0.8)	2.3 (0.9)
Gastrointestinal quality of life (36 [worst] to 180 [best])				
	130.0 (113.0, 141.0)	126.5 (109.0, 139.0)	135.0 (115.0, 148.0)	134.0 (120.0, 146.0)
	126.7 (18.8)	123.8 (20.2)	132.0 (20.6)	131.6 (20.5)
SF-36 scores (%)				
Physical functioning	70.0 (45.0, 90.0)	65.0 (40.0, 85.0)	75.0 (47.5, 90.0)	70.0 (45.0, 90.0)
	65.7 (27.4)	61.4 (28.4)	67.1 (27.7)	63.8 (29.0)
Role-physical	50.0 (0.0, 100.0)	25.0 (0.0, 75.0)	62.5 (0.0, 100.0)	25.0 (0.0, 100.0)
	46.4 (42.1)	36.4 (41.4)	54.4 (44.1)	46.2 (44.8)
Bodily pain	60.0 (40.0, 90.0)	57.5 (32.5, 90.0)	67.5 (45.0, 90.0)	67.5 (35.0, 90.0)
	61.3 (30.0)	58.2 (31.5)	64.3 (28.3)	62.1 (31.0)
General health	50.0 (35.0, 70.0)	50.0 (30.0, 70.0)	55.0 (30.0, 75.0)	50.0 (35.0, 70.0)
	51.2 (23.4)	50.3 (23.8)	52.8 (24.6)	50.6 (23.9)
Vitality	45.0 (30.0, 57.5)	50.0 (30.0, 60.0)	50.0 (25.0, 60.0)	50.0 (35.0, 65.0)
	43.9 (22.1)	42.7 (22.8)	45.6 (22.2)	46.7 (23.1)
Social functioning	62.5 (37.5, 75.0)	62.5 (37.5, 87.5)	75.0 (50.0, 87.5)	62.5 (37.5, 87.5)
	58.4 (28.8)	59.3 (31.6)	66.4 (28.6)	60.6 (31.7)
Role-emotional function	66.7 (0.0, 100.0)	33.3 (0.0, 100.0)	100.0 (0.0, 100.0)	83.3 (0.0, 100.0)
	58.4 (28.8)	59.3 (31.6)	61.7 (45.3)	60.2 (44.1)
Mental health	60.0 (44.0, 76.0)	64.0 (48.0, 76.0)	64.0 (48.0, 84.0)	64.0 (52.0, 76.0)
	60.3 (21.0)	60.8 (21.6)	62.7 (25.1)	63.0 (21.4)

Data are n (%), median (interquartile range) and mean (standard deviation).

Figure 13: Adjusted difference in means (95% CI) for FIQoL: PTNS vs. sham

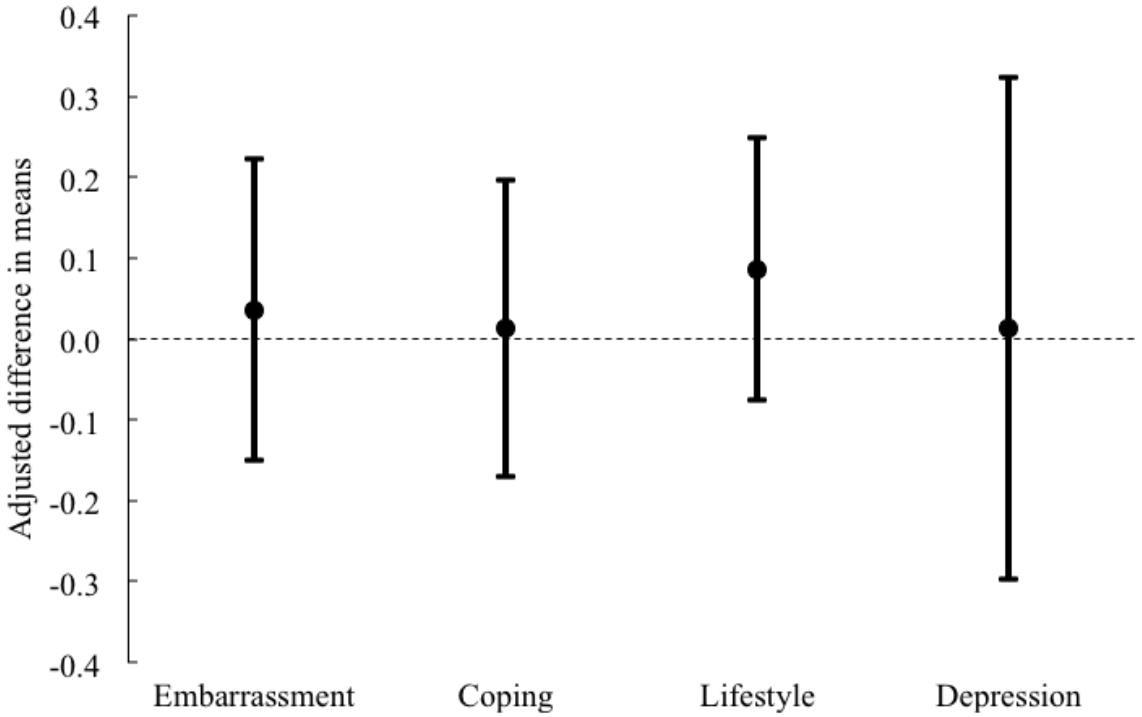
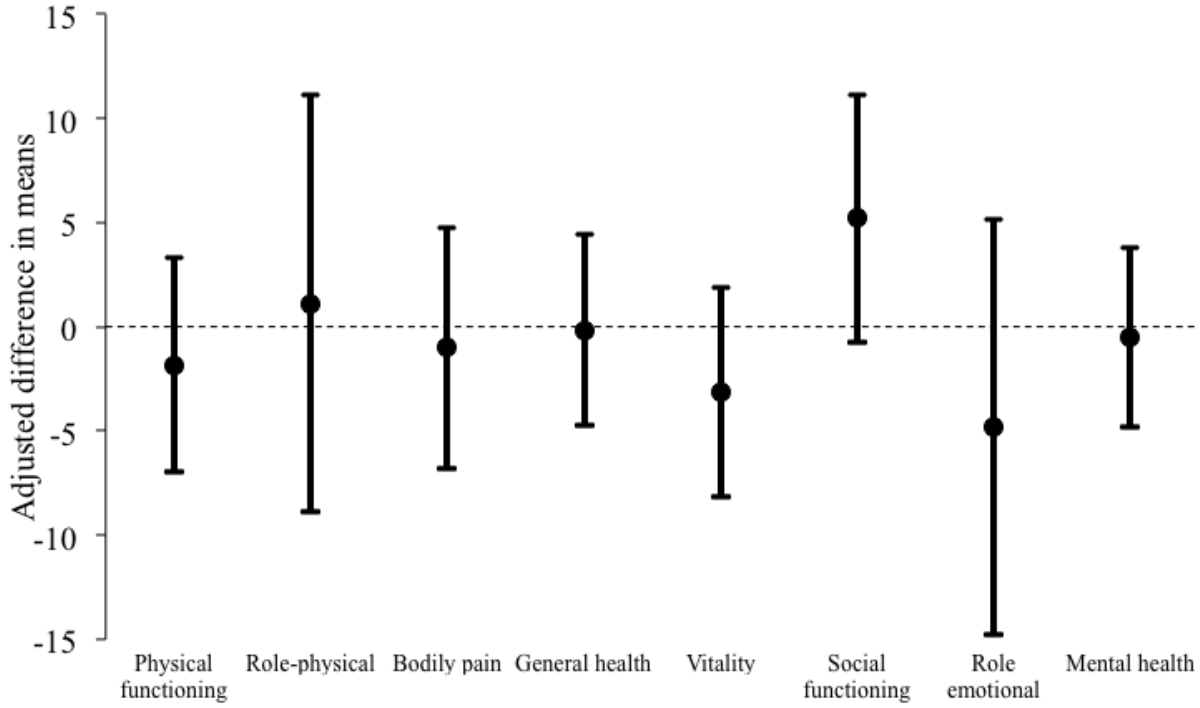


Figure 14: Adjusted difference in means (95% CI) for SF-36: PTNS vs. sham



4.4.6.5 Change in patient-centred outcomes score

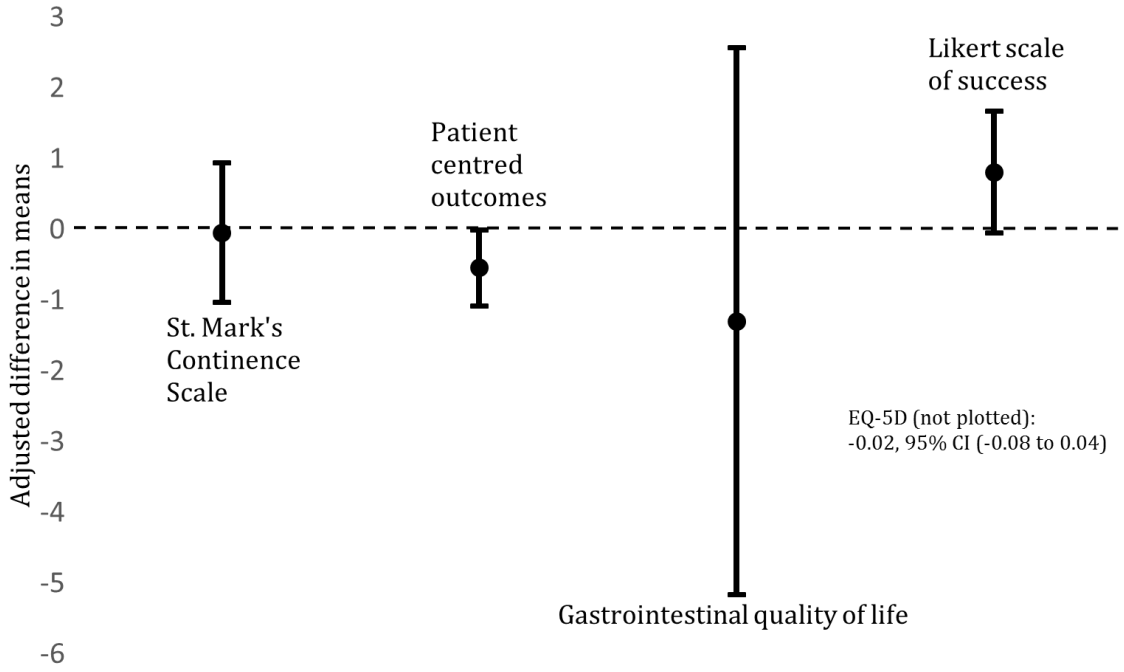
Improvement in patient-centred outcomes (i.e. a reduction in score) was significantly higher in the PTNS arm than the sham arm (difference in means -0.545, 95% CI (-1.081 to -0.008), p=0.047 (Table 15, Table 19 and Figure 15).

Table 19: Descriptive statistics for patient-centred outcomes at end of treatment

	Baseline		End of treatment	
	PTNS	**Sham**	**PTNS**	**Sham**
Patient centred outcomes	8.9 (7.8, 9.8)	9.2 (8.3, 10.0)	8.4 (6.9, 9.4)	9.3 (7.6, 10.0)
	8.5 (1.6)	8.7 (1.7)	7.8 (2.0)	8.4 (2.1)

Data are median (interquartile range) and mean (standard deviation).

Figure 15: Adjusted difference in means (95% CI) for other outcomes (SMCS, PCO, GIQoL, Likert scale of success and EQ-5D)



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

No significant difference existed in patients' global impression of success between the PTNS and sham arms (difference in means 0.808, 95% CI (-0.055 to 1.672), p=0.068) (Table 15, Table 20 and Figure 15).

Table 20: Descriptive statistics for Likert scale of success outcome at end of treatment

	PTNS	Sham
Likert scale of success	4.8 (0.0, 6.8)	2.1 (0.0, 4.9)
	4.0 (3.3)	3.2 (3.1)

Data are median (interquartile range) and mean (standard deviation)

4.4.6.7 EQ-5D analysis

There were virtually no differences between the two arms either at baseline or post treatment in respect of EQ-5D Index and VAS scores, with scores on both scales remaining unchanged over time (Table 15, Table 21 and Figure 15).

Table 21: Descriptive statistics for EQ-5D outcome at end of treatment

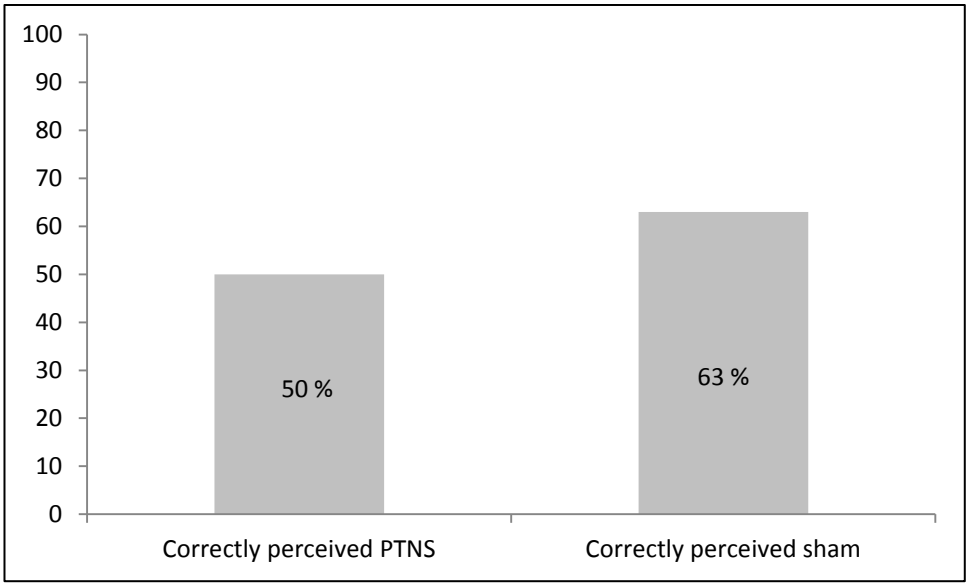
	Baseline		End of treatment	
	PTNS	Sham	PTNS	Sham
EQ-5D Index	0.69 (0.27)	0.63 (0.34)	0.68 (0.28)	0.65 (0.34)
EQ-5D VAS	64.50 (21.72)	64.04 (21.24)	64.25 (22.32)	63.69 (23.66)

Data are mean (standard deviation).

4.4.6.8 Other outcomes

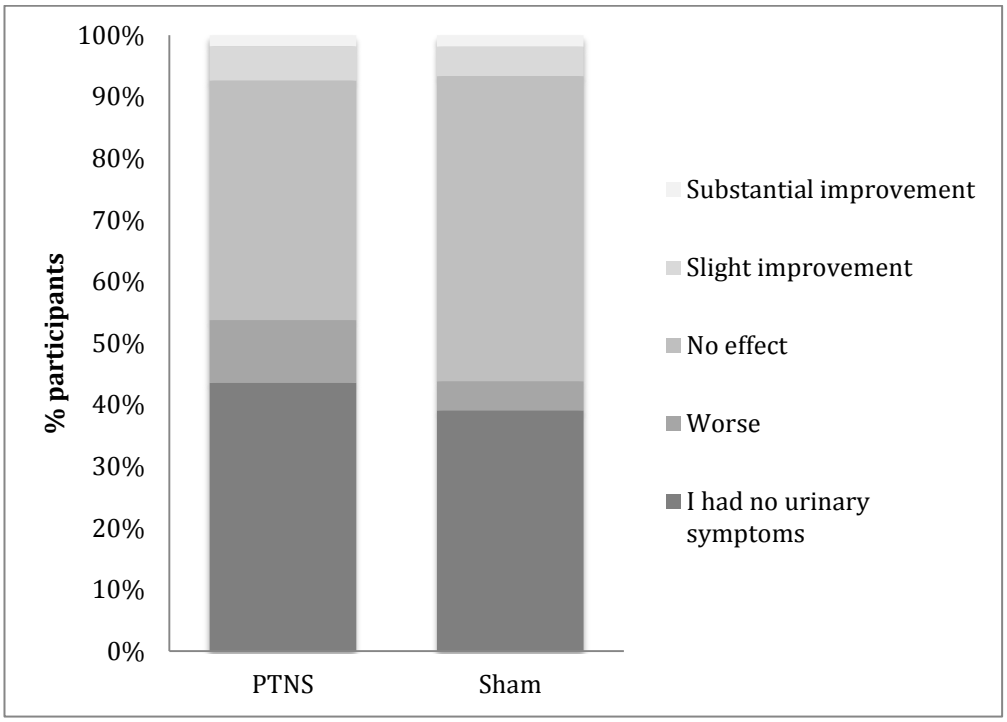
In the PTNS arm, 57/107 (54%) patients thought they had received PTNS and 48/107 (46%) thought they had received sham. In the sham arm of the trial, 32/103 (31%) patients thought they had received PTNS and 71/103 (69%) patients thought they had received sham. Of the 208 patients who completed this question, 56% of these perceived correctly (Figure 16). This proves that the sham arm was of a good standard.

Figure 16: Patients' perception of treatment.



Only 13% (8/61) of patients in the PTNS arm had slight or substantial improvement in urinary symptoms and similarly 11% (7/64) reported this in the sham arm. Most symptomatic patients reported no effect, 39% in the PTNS arm and 50% in the sham arm. Indeed more patients in the PTNS arm reported a worsening of urinary symptoms 10% vs. 5% in the sham arm (Figure 17).

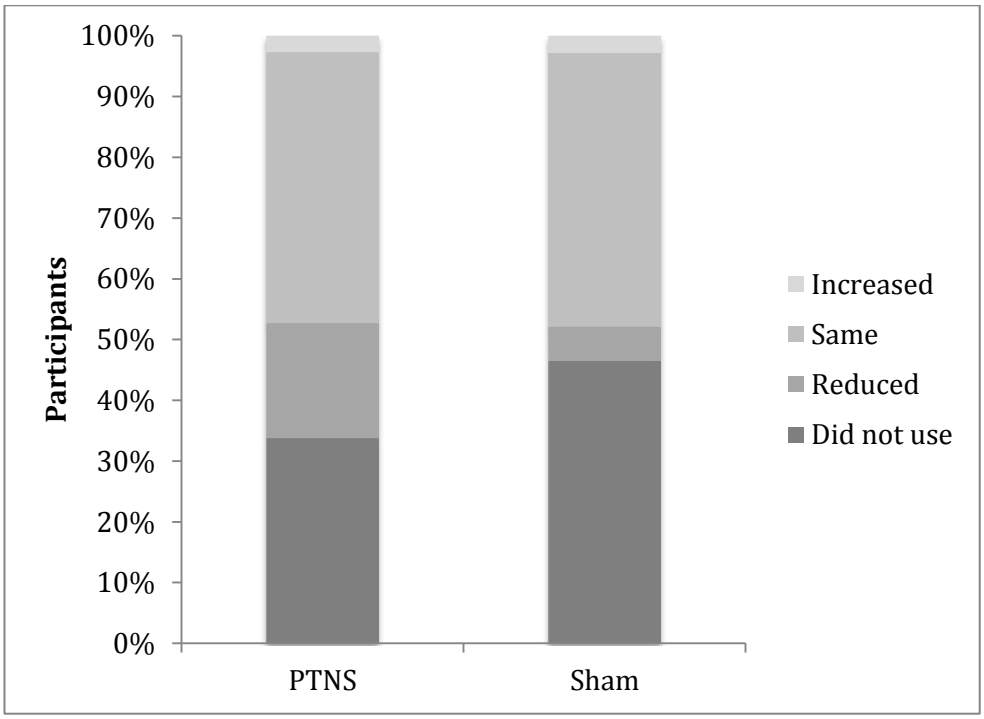
Figure 17: Effect of treatment on urinary symptoms



Of patients who used Loperamide at baseline, the majority in both PTNS (33/49=67%) and sham (32/38=84%) arms reported no change in use throughout the trial. Similar proportions in each arm (4% in PTNS vs. 5% in sham) reported increasing Loperamide use. A higher proportion of patients reduced their Loperamide use in the PTNS arm compared to the sham arm (29% vs. 11%, p=0.06) (Figure 18).

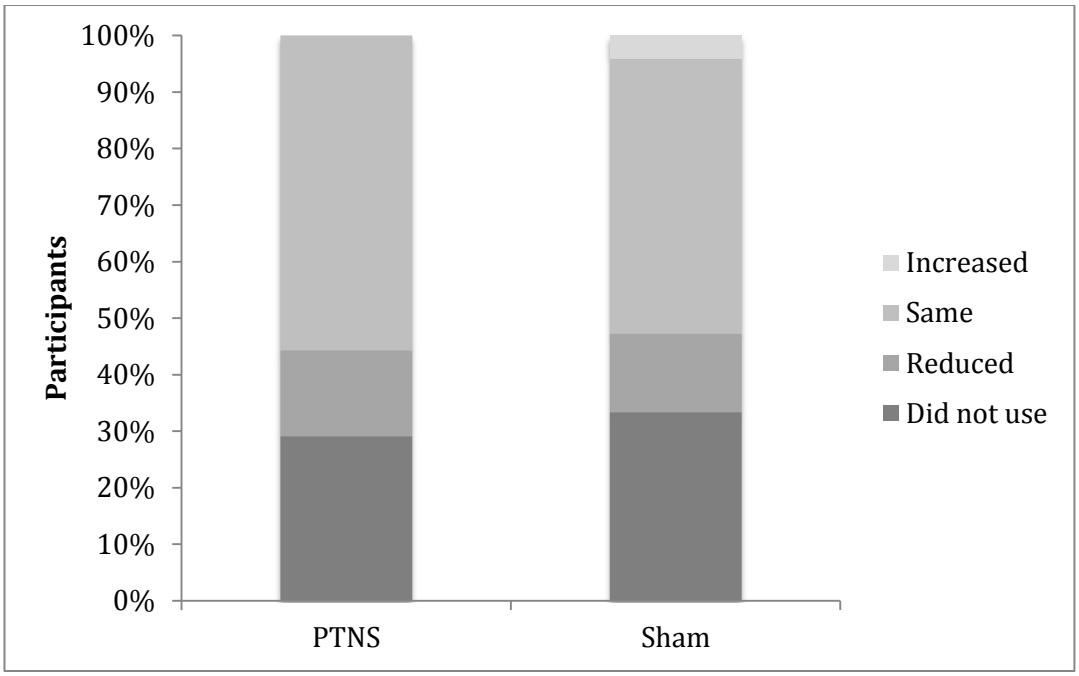
There was minimal concomitant medication usage and this has not been considered significant.

Figure 18: Effect of treatment on Loperamide use



Of the patients who used incontinence pads, the majority (56% (44/79) in PTNS arm and 49% (35/72) in sham arm) reported no change in use over the period of the trial. Similar proportions of patients reduced their pad usage through the course of the trial (15% in PTNS arm and 14% in sham arm), whilst 4% patients in the sham arm had to increase their pad usage compared with none in the PTNS arm (Figure 19).

Figure 19: Effect of treatment on incontinence pad usage



4.4.7 Per protocol analysis

Per protocol analysis was carried out subsequent to the intention-to-treat analysis. To be included in these analyses, patients were required to have at least 10 treatments within 13 weeks, with 10 treatments no less than 5 and no greater than 10 days apart. This was to ensure patients attended for treatments regularly and in a timeframe evenly spread throughout the treatment duration. One hundred and ninety seven of the 227 patients completed the treatment 'per protocol'.

Table 22 presents the results of this analysis. The conclusion from the analysis of the primary outcome remains unchanged and other important outcomes remain

unchanged apart from the Likert scale of success, which shows that those in the PTNS arm felt treatment was more successful than those in the sham arm; this was statistically significant.

Table 22: Results of per protocol analysis (n=197)

Outcome	**Odds ratio**	**95% confidence interval**	**p-value**
Percentage reduction in weekly FIE			
≥ 50% (primary outcome)	**1.269**	**0.688, 2.341**	**0.446**
≥25%	1.247	0.698, 2.228	0.456
≥75%	1.631	0.781, 3.409	0.194
100%	1.658	0.590, 4.655	0.338
Outcome	**Difference in means**	**95% confidence interval**	**p-value**
Change in weekly FIE			
Total	-2.233	-4.275, -0.191	0.032
Urge	-1.486	-2.778, -0.194	0.024
Passive	-0.600	-1.663, 0.463	0.268
St. Mark's continence score	0.202	-0.855, 1.258	0.708
GI QoL	-1.750	-5.864, 2.364	0.401
Faecal Incontinence Quality of Life			
Embarrassment	0.059	-0.141, 0.260	0.563
Coping	-0.007	-0.211, 0.196	0.944
Lifestyle	0.093	-0.079, 0.266	0.286
Depression	0.030	-0.302, 0.361	0.853
SF-36			
Physical functioning	-0.601	-5.964, 4.761	0.826
Role-physical	1.562	-9.062, 12.186	0.772
Bodily pain	-2.933	-8.975, 3.108	0.341
General health	0.612	-3.989, 5.213	0.794
Vitality	-2.872	-7.967, 2.224	0.268
Social functioning	5.665	-0.518, 11.848	0.074
Role emotional	-6.562	-16.988, 3.863	0.216
Mental health	-0.300	-4.633, 4.033	0.892
Patient centred outcomes	-0.593	-1.141, -0.044	0.034
EQ-5D index score	-0.020	-0.082, 0.042	0.524
Likert scale of success	0.934	0.037, 1.831	0.042

4.4.8 Subgroup analyses

Pre-planned subgroup analyses were performed for the primary outcome only. The following subgroups were selected:

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

The primary outcome was negative for each of these subgroup analyses (Appendix 2).

4.4.9 Sensitivity analysis

Sensitivity analysis was carried out, removing the patients who scored 'zero' on their initial bowel diaries (Appendix 3). This excluded 16 patients, 9 from PTNS and 7 from sham arms. The primary outcome was negative for this analysis (odds ratio 1.325, 95% confidence interval (0.736 to 2.385), p=0.348).

Further sensitivity analysis was carried out excluding patients who were recruited from poorly recruiting centres (defined as centres recruiting fewer than 5 patients) (Appendix 3). This excluded 4 patients from 2 centres, 2 from each arm. The primary outcome was negative for this analysis (odds ratio 1.234, 95% confidence interval (0.693 to 2.196), p=0.476).

4.4.10 Centre effect

Data were analysed to allow for a centre effect i.e. that outcomes amongst patients being treated by the same study centre may be correlated; indicating treatment at some centres may be more effective. The intra-centre coefficient (ICC) for the primary outcome based on the raw data was 0.01, 95% CI (-0.06 to 0.08) i.e. the variation in the

primary outcome between centres was very small indeed. In the results of the model where centre was included as a random effect and other variables as fixed effects the ICC was even smaller (<0.001). This indicates no significant centre effect.

4.4.11 Serious adverse events

There were four serious adverse events (SAEs) during the trial (Table 23). None were related to the trial treatment and all were resolved.

Table 23: Serious adverse events

SAE	Allocation	Grade	Duration (days)	Action	Relatedness	Outcome
Flexible cystoscopy for botox	PTNS	Moderate	3	H	U	R
Sleeve gastrectomy	Sham	Severe	1	H	U	R
Pilonidal abscess	Sham	Moderate	26	H	U	R
Shoulder manipulation	PTNS	Severe	1	H	U	R

H=hospitalisation, U = unrelated, R = resolved

4.4.12 Adverse events

A total of 204 adverse events were noted in the trial, 107 in the PTNS arm and 97 in the sham arm. Table 24 reports severity by relatedness in each arm. There were 7 mild related adverse events in each arm.

Table 24: Adverse events - severity by relatedness

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

Related and possibly related adverse events can be seen in Table 25.

Table 25: Related and possibly related adverse events

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

4.5 Discussion

4.5.1 Summary of results

No clinically significant benefit of PTNS over sham electrical stimulation was demonstrated in the treatment of adults with faecal incontinence. This was manifest by the primary outcome, with 38% patients in the PTNS arm and 31% in the sham arm achieving at least a 50% reduction in weekly FIE.

However, although there was no significant difference in the proportion of patients achieving this 50% or greater benchmark, PTNS did result in a significant reduction in mean total weekly FIE and mean urge weekly FIE compared to sham. Whilst statistically significant, the clinical interpretation of these findings is uncertain, since a reduction from a mean of 6.0 (IQR 2.0-4.0) to 3.5 (IQR 1.0-10.0) weekly FIE may or may not be helpful to patients. The clinical significance of a seemingly beneficial effect of PTNS compared to sham, of urge over passive FIE is also complex, since only a minority (in trial 23%) of patients had isolated urge FI.

Whilst PTNS also resulted in an improvement in the patient centred outcomes (a short-form derivative of the validated ICIQ-B[264]), this was not supported by the St. Mark's Continence Score, in which there was no significant improvement in the PTNS compared to the sham arm. There was also no significant improvement in disease-specific or generic quality of life measures.

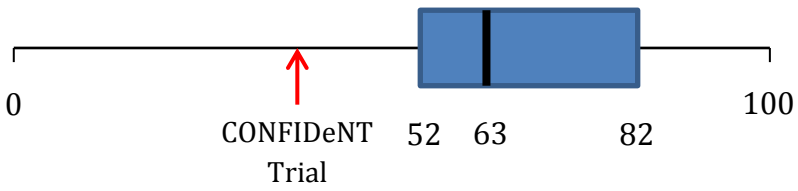
This study was generally conducted to a high standard and there were no major methodological flaws or protocol violations. The effect of sham stimulation was correctly predicted at 35%. It would have been difficult to predict such a marginal treatment effect based on the previous literature, however the effect of treatment was still less than our conservative estimate of 55%. The data however indicate the sample

size was adequate as the 95% CI of the primary outcome analysis precludes a clinically significant reduction in the odds of success.

4.5.2 Comparison of results to previously published studies

Results of this study may seem surprising when considered in the context of other published studies of PTNS in the treatment of FI, as discussed in Chapter 3, which include six case series, [235] one small single-centre randomised single-blind trial (PTNS vs. TTNS vs. sham),[225] one comparative case-matched study (PTNS vs. SNS)[265] and one prospective clinical audit comparing PTNS and SNS[266] and allude to a 52-82% response rate using the same primary outcome, which is considerably higher than the 38% reported here (Figure 20). The effect size seen in the treatment arm is nearer to that reported by a recent pilot randomised study (n=40) of PTNS vs. SNS, where 47% of patients had treatment success in the PTNS group at 3 months.[267] It also mirrors results from a large RCT of transcutaneous tibial nerve stimulation (TTNS) vs. sham electrical stimulation for the same indication, in which no superiority of TTNS was observed. [260] These findings highlight the necessity of conducting well-designed randomised controlled trials to answer clinical questions.

Figure 20: Percentage success rates of PTNS in published studies



In order to directly compare results of the CONFIDeNT Study with the previous literature, post hoc calculation of changes in mean weekly FIE and SMCS before vs. after treatment has been performed. In the PTNS arm, there was a significant reduction in mean weekly FIE after vs. before treatment ($p<0.001$), however there was no significant reduction in mean SMCS ($p=0.171$). Comparison of these findings to the previous literature is in agreement in terms of the weekly FIE however almost all studies demonstrated a reduction in the CCIS (which is similar to the SMCS). It is not clear why no improvement in SMCS was seen in The CONFIDeNT Study. Consideration has been given to the differences between the SMCS and the CCIS (CCIS does not include urgency or the use of constipating agents). The CCIS can be derived from the SMCS, and basic analysis of the SMCS (raw un-imputed data) with the omission of the final 2 questions (i.e. leaving the 5 questions covered by CCIS) results in an identical conclusion i.e. pre-intervention score (mean 11.3, SD 3.3) vs. post-intervention score (mean 10.6, SD 3.7).

Changes in quality of life measures, both in the previously published literature, and in the CONFIDeNT Study, showed no significant or reproducible improvement. This is interesting and merits discussion, since in the published case series literature, the lack of apparent improvement in quality of life is at odds with the other positive outcomes reported. One might have expected that if weekly FIE were reducing and CCIS improving, quality of life would follow suit. This was not observed. My hypothesis is that either the QOL tools used were not sensitive to change in FI, or that reduction in symptoms, although statistically significant, was insufficient for patients to lead a normal life. Indeed it may be that changes in quality of life take some time to achieve and it is not until patients are completely symptom free and have been for some time, that they have the confidence to report normalised activities. There is also the possibility that due to the unpredictable nature of FI, quality of life in this condition will never improve whilst there is always the possibility of an unexpected episode

occurring i.e. that fear continues to influence QOL reporting in some domains even after symptoms have started to resolve.

PTNS is also used to treat overactive bladder (OAB). There are two double-blinded RCTs that compare PTNS with sham electrical stimulation in the treatment of OAB, and both showed a statistically significant improvement in urinary frequency and urge urinary incontinence in the active PTNS arm compared to the sham arm (71% vs. 0% responders in the smaller study (n=35) $p<0.001$[268], and 54.5% vs. 24.9% $p<0.001$ in the larger pivotal trial[257] (n=174)). Both of these studies reported a higher treatment effect of PTNS than seen in the CONFIDeNT trial, and one that is significantly beneficial compared to sham.

4.5.3 Limitations

Despite the controlled design of this study, limitations are acknowledged. As discussed in detail in Chapter 3, there is no perfect or universally accepted outcome measure for FI[269]. The categorical measure of a ≥50% reduction in weekly FIE was chosen as the primary outcome measure. Although subject to criticism, this outcome was chosen since it is widely used to assess SNS, thus allowing comparisons to be drawn between the two treatment modalities. Also, the 50% criterion has been applied as the primary endpoint in both the pivotal trials of contemporary treatments in FI[270, 271]. It is accepted that the choice of another, perhaps less stringent primary outcome measure may have resulted in a different conclusion, however if other treatments for the same condition are assessed using this outcome, and meet it, it is important that PTNS is assessed against this benchmark.

Consideration of patient selection is important. As is the nature of faecal incontinence, there was heterogeneity in the population of patients selected to take part in the trial. This heterogeneity encompassed patients with urge, passive or a mixed picture of

faecal incontinence, and included some patients who suffered with frequent loose stools, and a significant proportion (approximately 40%) who had concomitant problems with rectal evacuation (see Chapter 5). In addition to this, all patients received prior conservative therapy but this was not formally standardised reflecting the lack of consensus on what constitutes a minimum standard in the UK. Thus a pragmatic view was adopted that balanced some heterogeneity in baseline characteristics (e.g. type of faecal incontinence symptoms and degree of treatment refraction) with exclusion of other specific patient subgroups that might have differing response rates. These exclusions included patients with inflammatory bowel disease, who would be more likely to suffer, for example, with uncontrolled diarrhoea. This pragmatic design was important to adequately assess PTNS as a first line treatment for FI, for example in GP surgeries or nursing homes, where rigorous patient selection would not be feasible or possible. Some efficacy was demonstrated in reducing urge FI episodes, and this has been previously documented [235,251] and is akin to the approved indication for PTNS to treat overactive bladder.[257] However to determine whether targeted selection of patients with this baseline characteristic (or others) would lead to a different conclusion would require validation in an appropriately designed study. Overall, it is acknowledged that results can only be considered valid for the population studied at the point of intervention in the algorithm of care.

For similar pragmatic reasons, anti-diarrhoeal medication use was not prohibited (concern that unrecorded usage would continue). Consideration has to be given to the fact that a differential change in anti-diarrhoeal medication between the two groups may have reduced the effect size of PTNS. The decision was made to record patients' Loperamide usage throughout the trial, rather than restrict it. Patients were asked each week about Loperamide usage, however following the first meeting of the TSC and DSMC, it was felt this was not accurately recalled by patients, and a decision was made to instead ask patients at the end of the trial whether their usage had remained the

same, increased or decreased. Since this decision was made partway into the trial, this information was not collected from all patients. The question on Loperamide usage was answered by 144/227 patients (64%), and this was in the main due to 55 patients having completed the trial prior to implementation of the new questionnaire. Those who did answer the question were evenly balanced between treatment arms. Of those who were taking Loperamide, almost three times as many patients in the PTNS arm reduced this compared to the sham arm. Post-hoc Chi-square testing found weak evidence of a difference in Loperamide use (p=0.06). Although this could have confounded the effect size this would have been unlikely to affect the overall trial conclusion based on the primary endpoint. This calculation should however be interpreted with caution as the numbers using Loperamide at baseline were comparatively small, and, since they are not the full randomised samples, may differ systematically.

Another criticism of this study could be that patients were not excluded on the basis of having 'zero' faecal incontinence episodes reported on their baseline bowel diary, so long as the principal investigator was convinced of the fact that the patient had 'faecal incontinence significant enough to warrant intervention'. This decision was taken as faecal incontinence is often a problem which happens in 'bouts' and it is not impossible for a patient to experience 2 symptom free weeks by chance. The alternatives would have been either to exclude these patients (an ethical issue in patients with significant FI), or to give patients another chance to complete the bowel diary. The latter would have risked the introduction of bias i.e. first, enthusiastic patients might fabricate a second bowel diary to merit inclusion and secondly, the randomness of baseline observations would have been compromised by selection bias. Sensitivity analysis was done removing the 16 patients to whom this applied, who did happen to be spread evenly across the two arms, and this made no difference to the overall results.

Quality assurance measures aimed to minimise variation in intervention performance but this could have contributed to differences from previously published experience in single expert centres. [235, 251] However, although disparity existed amongst centre recruitment rates (range 1-45 patients), sensitivity analysis excluding low-volume centres did not change the primary outcome. In addition, no significant centre effect was observed in analysis of the primary outcome.

A final limitation is the short follow-up period. It is fully acknowledged that effectiveness of FI treatments cannot be judged adequately without a longer interval of follow-up e.g. 1 year. The longer-term effectiveness of PTNS was not an objective of this trial, however a further study following up all patients in this study, has been performed, and is presented in Chapter 6.

4.5.4 Interpretation of results in context of previous published literature

There is disparity between the CONFIDeNT Trial findings and the published literature on PTNS in the treatment of FI. No double blind RCT of PTNS vs. sham had been performed before CONFIDeNT, and it is likely that the disparity may be accounted for by study design.

The CONFIDeNT Study included a sham group to negate the effect of natural change in disease status over time and the well-recognised effect of nurse-led face-to-face intervention.[272] It is widely acknowledged that placebo responses are disproportionately high in patients with chronic debilitating GI conditions due to a high level of expectation.[260] Meta-analyses of 45 published trials estimates the placebo response rate in functional dyspepsia at between 6% and 72%[273, 274], and that of 50 placebo controlled irritable bowel syndrome trials between 3% and 84%[275-277]. A recent multicentre phase II double blind randomised placebo controlled investigation of NRL001 (an alpha1-adrenoceptor agonist), demonstrated treatment success (using

both FIE and CCIS as outcomes) in 35% of the placebo arm (i.e. much higher than the 25% they had anticipated), drawing the conclusion that any studies without a placebo or comparator arm should be interpreted with caution. The CONFIDeNT Study correctly estimated the placebo response at 35% (vs. 31% found).

Selection bias in case series is a problem unless subjects are truly selected consecutively. In addition to this, case series are often subject to attrition bias as patients may be lost to follow up or researchers may selectively report only in subjects with positive findings. In case series, both the patient and the observer are often unblinded. This can introduce bias from both perspectives: patients may experience a high level of expectation, which may influence reporting; and in addition to this, bias may be introduced from the observers' perspective, since clinicians often have a vested interest in treatment and publication. Without the rigour of an independently managed trial, bowel diaries can also introduce bias if they are unmasked and subject to investigator interpretation[269].

The CONFIDeNT Study represents Oxford Level Ib evidence[278], likely reflecting more reliable data than the Level IV literature published before. This would not represent the first time a small body of low-level literature indicates a treatment to be successful, only for a definitive trial to contradict this. Indeed, a handful of case series intimated that SNS may be useful in the treatment of constipation, however a recently published definitive trial has shown this not to be the case[279].

The disparity of The CONFIDeNT trial findings with the randomised controlled trials of PTNS to treat OAB could be due to a number of reasons. Firstly, it could simply be due to PTNS having efficacy in OAB but not FI. Alternatively it could be due to these studies selecting purely patients who had overactive bladder (OAB) i.e. who experience bladder urgency (more akin to faecal urgency or urge faecal incontinence), which may

account for the CONFIDeNT trial showing no overall benefit in patients, but significant reductions in urge faecal incontinence episodes.

The disparity could also be a factor of primary outcome measure selection. Peters *et al.* used a subjective primary endpoint involving number of patients who graded their overall bladder symptoms as moderately or markedly improved on a global response assessment (GRA)[257].

Both published urological RCTs also reported a significantly lower treatment effect of the sham. The placebo effect in trials of functional bowel disease is well-acknowledged to be high, as mentioned previously. This may indicate the 0% placebo effect in the Finazzi-Agro[268] trial is a product of a small sample size, inadequate blinding, or both. The apparently lower sham response in both studies may also have resulted from a less realistic sham. The sham stimulation used was different between these urological studies and also different from that used in the CONFIDeNT trial. In one study, the needle was placed in the medial head of gastrocnemius muscle and electrical stimulation only activated via the needle for 30 seconds prior to the stimulator being turned off[268] and in the other, the ankle was chosen but a Streitberger needle used, which does not pierce the skin, and electrical stimulation delivered via TENS. The sham chosen in the CONFIDeNT trial was designed to give a very similar feeling to that produced by the active treatment, by giving the sensation of the skin being pierced by the needle and by providing a constant electrical sensation. This sham was a modification of that used in the Peters *et al.* study of OAB but notably improved on the Streitberger approach by using the supplied Uroplasty needle and piercing the skin so to give the same sensation as the PTNS arm (the only difference was the needle was not advanced beyond the superficial subcutaneous tissue). The sham was shown not to stimulate the tibial nerve during neurophysiological testing.

4.5.5 Other interpretive consideration

4.5.5.1 Placebo responses

The first published work on the therapeutic effects of placebo reported up to 35% of 1082 patient having symptomatic pain relief[280]. This paper was subsequently criticised, with the view that true study of the placebo effect should not compare the before and after treatment in the placebo arm of a randomised controlled trial, but the difference between a group randomly allocated to placebo and a group randomly allocated to no treatment, since observed differences may be due to natural history of the disease (spontaneous improvement or fluctuation of symptoms in a chronic disease) or regression to the mean i.e. the tendency for extreme measurements to become closer to the mean when repeated[281]

Following a Cochrane review[282] of randomised controlled trials including a placebo group and a non-treatment group, where very different placebo response rates were obtained, a recommendation was made that studies into the placebo effect should be studied in a disease or group of diseases[283].

The most powerful documented placebo effect is in chronic pain syndromes. In one study, the cholecystokinin antagonist proglumide was a better analgesic than placebo, which in turn was better than no treatment at all. Hidden injection of proglumide (which the patient was unaware of) however, was a completely ineffective analgesic. Thus the interpretation for the mechanism of action of proglumide was that it acts on expectation pathways and enhances the placebo analgesic response, rather than acting on pain pathways[284]. A better method of conducting a trial to define the efficacy of a pain medication has been suggested; this involves an 'open–hidden paradigm'[285] where medical treatments are given covertly so that the true response can be observed, eliminating the chance of an enhancement of the 'expectation pathway'.

Unfortunately, adoption of an 'open-hidden paradigm' methodology would not be possible in a trial of an intervention, since administration would not be possible without patient awareness.

Work reporting the placebo effect in Parkinson's disease raises the concept of 'expectation and the subsequent neurobiological changes'[285]. A double-blind study on human fetal mesencephalic transplantation for Parkinson's disease found that the patients' perceived allocation (either active treatment or placebo) had a more powerful impact on both quality of life and motor function than did the actual treatment. A study on pain subsequently found perceived assignment in an acupuncture trial had a greater impact on the analgesic outcome than did the actual treatment[286].

Post hoc analysis of treatment success (using the primary outcome) is possible for the CONFIDeNT Study data by grouping patients by 'perceived outcome group' rather than actual treatment group i.e. analysing the outcome of those patients who thought they had PTNS vs. the outcome of those patients who thought they had sham.

Eighty nine patients of the 227 in the trial thought they had received PTNS. Of these 89 patients, 40 had treatment success. This gives a success rate of 45% in the treatment arm. One hundred and nineteen of the 227 patients in the trial thought they had been allocated to sham. Of these 119 patients, 28 had treatment success. This gives a success rate of 24% in the sham arm. No formal statistical analysis was done on this, since it is a post hoc analysis, however this is highly likely to be significant given there is almost double the success rate in the 'perceived PTNS arm' compared to the 'perceived sham arm'.

Specificity of a placebo depends on the verbal cues given to the recipient e.g. placebos can have opposite effects on heart rate and blood pressure depending on what the recipient is told the effect will be[272]. Several authors have highlighted the importance of

the doctor-patient relationship in the placebo effect, specifically communication skills, time spent with the patient and the doctor's enthusiasm or attitude towards the effect – all of which produce a heightened placebo effect[272].

This is relevant to the CONFIDeNT Trial, since there was significant interaction with each patient and the practitioner delivering the treatment, as each patient attended for 12 consecutive weeks. The trial set-up aimed to ensure, however, that practitioner-patient interaction was identical in each group, by prescribing how the interaction was to take place. In this way, any effects of such interaction should be similar in both groups. Nevertheless, this could have had an effect in both groups, which had the mathematical effect of reducing the proportional difference in effect size between active intervention and sham

The nature of the placebo itself is also recognised to affect its efficacy. For example, 'operative interventions' have a larger placebo effect than do 'procedures' than in-turn do 'medications'. Intravenous medications evoke a larger placebo response than do oral medications. Also, the setting in which a procedure is carried out carries an effect on the placebo effect, e.g. a white coat or a hospital setting make a difference[272]. Again this finding is relevant to the CONFIDeNT Study, being an invasive (albeit minimally) intervention carried out in a hospital setting.

Consideration of the placebo effect in the CONFIDeNT Trial is slightly easier than some of the trials reported above, since 1) this trial was not designed to identify or quantify a placebo effect, and 2) this trial did not demonstrate a positive effect of the active treatment.

The inclusion of a 'no treatment' group in The CONFIDeNT Study would have been interesting, and would have allowed us to further analyse the placebo effect in FI, however it would not have helped in achieving the study aim, which was to assess

whether electrical stimulation of the tibial nerve resulted in an increased treatment effect in patients with faecal incontinence. In addition to this, there may well have been ethical issues with this trial design, since patients at this stage are already some way through the treatment algorithm.

4.5.5.2 Inclusion criteria and choice of outcomes

The CONFIDeNT Trial inclusion criteria were broad, including patients with FI from any cause; and with any combination of symptoms i.e. urge and/or passive FI, mixed FI/evacuatory dysfunction. Had we selected specific patient subgroups, the results may have been different. Subgroup selection, however, would have limited recruitment and if based on robust criteria would also have mandated more expensive and invasive testing e.g. formal anorectal physiology. A further factor would be generalisability of results had specific subgroups been selected. As discussed in Chapter 4.5.3 above, in the limitations of the CONFIDeNT Trial, a pragmatic approach to inclusion criteria was chosen.

The results of this trial could have reflected the primary outcome measure chosen. By this, I refer first to the use of bowel diaries as an outcome measure, and secondly to the way the bowel diary was used to select a primary outcome. Whilst the bowel diaries were completed well in this trial, they are subjective and rely on a patient completing them honestly and accurately (there is no reason, however, to suspect that they would not do this). Unfortunately, there is no objective outcome measure available for FI since all outcome measures are self-reported. To improve the accuracy and ease of using bowel diaries, an 'App' to record bowel diary information may make it more reliable and less open to interpretation. Such technology is not however currently available, and to have developed and provided this in a trial would have required user testing, validation and additional cost.

The chosen outcome of at least a 50% reduction in weekly FIE may have had an effect on the trial results. Had we based the primary outcome on the presence of a significant reduction in weekly FIE, this trial would have yielded a statistically positive result (total and urge FIE). However for the reasons explained above, it was decided that a percentage reduction was a more clinically meaningful result. In addition, this outcome could be used to 'benchmark' the effect of PTNS against other FI treatments, for example SNS. This target is obviously achievable, since studies of SNS show treatment success.

4.5.6 Clinical impact

The clinical implications of this trial merit discussion. The pragmatic design, including patients with FI due to any aetiology (excepting specific exclusions) and with any symptom pattern i.e. urge, passive or both, aimed to make results generalisable. Based on the evidence presented, it would be hard to recommend the use of PTNS as a treatment for such unselected patients; indeed this could not be justified.

PTNS does, however, seem to offer a treatment effect in almost 40% of patients, and what is unclear is whether this is a genuine biological effect not seen due to limitations in the study. Indeed, there are some people for whom their treatment response has been nothing short of miraculous.

In addition to this, PTNS is already embedded within the FI management algorithm in many UK and EU centres, and whilst this is only within the context of audit or research,[287] there are many patients for whom this treatment is highly successful (Figure 21). A relevant question is whether it is morally or ethically acceptable to withdraw this treatment based on the evidence presented here? Conversely, is it appropriate to continue funding a treatment whose effect size may be conferred largely by placebo? Could we exchange the costly PTNS with cheaper 'sham' delivered via

TENS since this has similar efficacy and much less cost? A compromise may be to judge treatment effect at six weeks, and only continue therapy in those who are successful at this time point.

Figure 21: Daily Mail Article[288]

Page 42 Good Health Daily Mail, Tuesday, August 27, 2013

Tiny needle in your ankle to stop those urgent trips to the loo

AROUND 10 per cent of the adult population suffers from faecal incontinence at some point. Patsy Collis, 70, a retired bank cashier from Bishop's Stortford, Herts, underwent a pioneering treatment for the problem, as she tells Anna Hodgekiss...

THE PATIENT

THREE years ago I began to develop dreadful stomach pains. At first, it tended to happen when I went out for a meal.

Gradually it got worse, happening every three days or so, and after a while I didn't even get any warning of needing to go to the loo. It made no difference if, or what, I'd eaten — there seemed no rhyme nor reason.

It got to the point where I was taking Imodium every day, but even that didn't really help.

My condition curbed my social life. In fact, I became a bit of a recluse — I couldn't go to the cinema or even dream of getting the train to visit my best friend in Hastings.

I only told a few people and while they were very supportive, it was still embarrassing and I felt ever so miserable.

Luckily, my GP was brilliant. I saw her after a month when I realised it couldn't just be down to something I'd eaten. She put me in for tests and referred me to the Royal London Hospital in Whitechapel. They thought it might be stomach or bowel cancer, but thankfully the tests were clear.

It was eventually suggested that even though it had been 44 years before, it could have been the birth of my son Peter that had caused problems with the nerves and muscles in that area — and these problems were only showing up now.

It seemed unlikely to me, as it

medical expert. The consultant suggested I join a trial of a new treatment where they put a tiny needle into your ankle, and send electrical impulses to the nerve that controls the bowel and surrounding muscles.

It would mean I wouldn't have to go to the loo so often, and would also hopefully kick-start the sensation of needing to go, so I'd have some

ME AND MY OPERATION

ANKLE STIMULATION FOR FAECAL INCONTINENCE

— just to go to hospital twice a week for six weeks for a half-hour session.

I couldn't really see how a jab in the

injury to the muscles and nerves of the pelvic floor and anus.

In some this will lead to inconti-

Picture: RANN CHANDRIC

Over the moon: Patsy Collis says she has got her life back

patients. It's not a miracle cure — it requires two operations, the initial costs are around £10,000 per patient, and some complica-

Results do indicate efficacy of PTNS in reducing weekly FIE and preferentially weekly urge FIE. This has been previously documented[235,251] and is akin to the approved indication for PTNS to treat overactive bladder.[257] It may be that there are characteristics about those who are experiencing treatment effect, which could help improve patient selection and therefore improve treatment results. Further analysis of the CONFIDeNT Trial data is undertaken in the next chapter. What is certain, however, is that further studies are required to determine the efficacy of PTNS within subgroups e.g. those with urge FI. Health service research could also usefully determine how PTNS promotes or contributes to other mixed packages of nurse-led care.

5 Predictors of outcome in the CONFIDeNT Study

5.1 Introduction

The CONFIDeNT Study yielded a negative overall result i.e. for the population studied and with the primary outcome chosen, there was no significant benefit of PTNS over sham electrical stimulation in the treatment of faecal incontinence. However, 38% of patients did have successful treatment with PTNS. As discussed in the previous chapter (Section 4.5.1) this study was pragmatic and included all patients with FI regardless of aetiology. There is a possibility that specific sub-groups of patients could benefit significantly from PTNS, this requires further exploration.

The results of the CONFIDeNT Study, along with previous literature indicate patient subgroups which may demonstrate increased benefit with PTNS treatment. Given that there were some positive secondary outcomes, namely a greater reduction in mean total weekly FIE in the PTNS group compared to the sham group, which included a greater reduction in urge rather than passive faecal incontinence episodes, it may be that the presence of urge FI is predictive of a successful outcome. Since the majority of patients presented with both urge and passive FI, the possibility that isolated urge FI or faecal urgency are predictive is also a possibility and a previous study supports this theory [251].

There are factors generally relevant to the selection of FI patients, namely sex, age and severity of FI, and these warrant investigation. Indeed, many clinicians believe those patients with severe FI will not benefit from non-invasive treatments, and should advance directly to surgical management strategies. Many people use a cut-off of at least daily episodes of FI (i.e. ≥7 FIE per week) to denote severe disease, and it seems logical to test this.

There is a high prevalence of rectal evacuatory dysfunction amongst the FI patient population[151, 289], and this was also apparent in the CONFIDeNT Study. The effect of problematic rectal evacuation on the efficacy of PTNS in the treatment of FI is unknown. Whilst one study has shown PTNS to be effective in the treatment of chronic constipation[290], a recent trial of SNS has refuted the effectiveness of this mechanistically similar therapy in the treatment of constipation[279]. It is therefore important to include this as a factor in the sub analysis of the CONFIDeNT Trial results.

5.1.1 Study Aims

The aim of this study was to identify baseline predictors of PTNS outcome at the 14 week assessment.

5.1.2 A priori hypotheses

As discussed in the introduction, there are several reasonable hypotheses that merit testing as predictors of PTNS outcome based on the primary outcome measure of treatment success as defined in the CONFIDeNT Trial (i.e. ≥50% reduction in weekly FIE), at the 14 week assessment. These include:

FI symptom characteristics that may have a beneficial outcome:

- Urge faecal incontinence
- Isolated urge faecal incontinence
- Faecal urgency

Other baseline characteristics whose effect on outcome is not apparent from primary CONFIDeNT analysis:

- Sex
- Age
- Severity of FI

- Co-existent rectal evacuatory difficulty based on symptom reporting

There were a number of other recorded baseline characteristics which could be predictive of outcome to PTNS treatment, but which were either too infrequent to enable analysis or inadequately captured in baseline assessments:

- Lack of intractability to previous treatments
- Absence of irritable bowel syndrome
- Absence of psychological morbidity
- Ability of patient to defer defaecation (measured in minutes)
- Co-existent rectal evacuatory disorder based on objective radio-physiological testing

5.2 Methods

5.2.1 Study population

Data from all patients who received PTNS in the CONFIDeNT Study formed the study population.

5.2.2 Methods

Based on the above hypotheses, the following variables were investigated:

- Urge faecal incontinence (presence or absence)
- Isolated urge faecal incontinence (presence or absence)
- Faecal urgency (presence or absence)
- Rectal evacuatory difficulty (presence or absence)
- Sex (male or female)
- Age (≥ or < 58 years)
- Severity of FI (≥ or < 7 weekly FIE)

The presence of rectal evacuatory difficulty was defined as presence of any of the following symptoms during structured interview at baseline: patient perceived difficulty in rectal evacuation, excessive straining, the requirement of regular digitation or the sensation of incomplete emptying. These factors relate to questions from validated scoring systems for constipation and/or obstructive defaecation, including Longo's ODS scoring system[291] (straining, incomplete emptying and digitation) and Cleveland Clinic Constipation Score[292] (incomplete evacuation, digitation).

Patients' age was categorised around the median age in the trial population of 58 years. The patients were divided into those under the age of 58, and those aged 58 or older. FI severity was categorised into those with at least daily episodes of FI compared to those with less than 7 FIE per week.

5.2.3 Statistical analysis

Preliminary univariate logistic regression analysis was performed for each of the selected baseline variables. A p-value of <0.1 was selected to indicate a significant relationship.

To analyse the presence of co-linear relationships between the above factors, multivariate logistic regression analysis, using all the variables listed above, was subsequently performed.

Data were presented as odds ratios (OR) with 95% CI. A p-value of <0.05 was considered to indicate statistical significance. All analyses were performed with proprietary software (IBM SPSS Statistics Version 22, NY, USA).

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5.3 Results

5.3.1 Univariate analysis

Univariate logistic regression analysis of the baseline characteristics of patients who received PTNS in the CONFIDeNT Trial included 103 patients. The number of patients with each baseline characteristic, along with rates of treatment success, and results of the univariate logistic regression analysis are presented in Table 26.

Table 26: Univariate analysis of CONFIDeNT Trial results

Symptom		N (%)	Success n (%)	Failure n (%)	p value	Odds ratio	Lower 95% CI	Upper 95% CI
Urge FI	Present	83 (80.6)	33 (84.6)	50 (78.1)	0.42	0.65	0.23	1.86
	Absent	20 (19.4)	6 (15.4)	14 (21.9)				
Isolated urge FI	Present	25 (24.3)	11 (28.2)	14 (21.9)	0.47	1.40	0.56	3.50
	Absent	78 (75.7)	28 (71.8)	50 (78.1)				
Faecal Urgency	Present	89 (89.0)	34 (91.9)	55 (87.3)	0.48	0.61	0.15	2.45
	Absent	11 (11.0)	3 (8.1)	8 (12.7)				
Rectal evacuatory difficult	Present	53 (53.0)	15 (39.5)	38 (61.3)	0.03	0.41	0.18	0.94
	Absent	47 (47.0)	23 (60.5)	24 (38.7)				
Sex	Male	9 (8.7)	4 (10.3)	5 (7.8)	0.67	0.74	0.19	2.95
	Female	94 (91.3)	35 (89.7)	59 (92.2)				
Age	<58	53 (51.5)	18 (46.2)	35 (54.7)	0.71	0.32	1.58	0.71
	≥58	50 (48.5)	21 (53.8)	29 (45.3)				
Severity of FI	< 7/wk	57 (55.3)	21 (53.8)	36 (56.3)	0.81	0.81	0.92	0.41
	≥7/wk	46 (44.7)	18 (46.2)	28 (43.8)				

The only predictor of an unsuccessful outcome with PTNS from the characteristics selected, was the presence of any form of rectal evacuatory disorder (odds ratio 0.41, 95% confidence interval 0.18-0.94, p=0.03).

5.3.2 Multivariate analysis

Subsequent multivariate logistic regression analysis was performed to explore the possibility of co-linear relationships between the selected baseline characteristics. Multivariate logistic regression analysis of the baseline characteristics of patients who received PTNS in the CONFIDeNT Trial included 97 patients (who had complete data sets for all chosen variables). The presence or absence of each characteristic at baseline is presented in Table 27 and the results of regression analysis in Table 28.

Table 27: Presence of baseline characteristics in PTNS group

Symptom		**N**
Urge FI	Present	80
	Absent	17
Isolated urge FI	Present	25
	Absent	72
Faecal Urgency	Present	86
	Absent	11
Rectal evacuatory difficulty	Present	51
	Absent	46
Sex	Male	9
	Female	88
Age	<58	51
	≥58	46
Severity of FI	< 7/wk	54
	≥7/wk	43

Table 28: Results of multivariate logistic regression analysis of PTNS group

Sympton	P-value	Odds ratio	95% CI	
			Lower	Upper
Urge FI	0.85	0.86	0.20	3.80
Isolated urge FI	0.18	0.47	0.16	1.41
Faecal Urgency	0.57	0.61	0.11	3.47
Rectal Evacuatory Difficulty	0.03	0.38	0.16	0.92
Sex	0.35	0.46	0.09	2.31
Age	0.20	0.56	0.23	1.37
Severity of FI	0.45	0.70	0.27	1.79
Constant	0.45	2.23		

The findings from multivariate logistic regression analysis confirm that the only baseline characteristic which affects the outcome of PTNS at 14 weeks the presence of rectal evacuatory symptoms (odds ratio 0.38; 95% confidence interval 0.16 – 0.92, p=0.03).

5.4 Discussion

5.4.1 Summary

Of the baseline characteristics selected for logistic regression analysis, only one was predictive for the outcome of PTNS in the treatment of FI at 14 weeks. In the population studied in the CONFIDeNT Trial, the presence of urge faecal incontinence, isolated urge faecal incontinence, and faecal urgency were not predictive of outcome for PTNS treatment. Age (≥ or <58 years), sex and FI severity (≥ or < 7 FIE/wk) similarly were not predictive of PTNS outcome. The absence of any rectal evacuatory difficulty at baseline, however, was highly predictive of a successful outcome with PTNS at 14 weeks in both univariate and multivariate analyses.

5.4.2 Predictors of outcome

The absence of any association between age, sex, severity of FI, presence of urge FI, isolated urge FI and faecal urgency with outcome of PTNS in the treatment of FI could be correct i.e. there is no association, or it could represent a type II error i.e. it may represent a false negative result. This finding may be a result of the number of patients in the analysis, since the logistic regression was only based on a maximum of 115 patients (those in the PTNS arm of the trial). To resolve this would require properly designed trials including patients on the basis of presence or absence of each of these factors, conducted in a similar way to the CONFIDeNT Study.

The association between co-existent rectal evacuatory difficulty and a negative outcome of PTNS in the treatment of adults with FI is very interesting and merits further discussion since it appears to significantly prejudice the outcome of the active intervention in the PTNS arm of the CONFIDeNT study. To assess whether this effect is one that was specific to the active intervention, we performed a further post hoc analysis of the sham arm of the trial using only this variable with the possibility that

patients with such symptoms either perform generally poorly to any intervention or that rectal evacuatory dysfunction has a specific biological effect making patients resistant to neuromodulation. The results of this analysis were also very interesting and confirm the widely held view that such patients, like those with other functional disorders e.g. IBS, have disproportionately high placebo responses.

Univariate logistic regression analysis was thus performed on those patients who had sham treatment in the CONFIDeNT Trial, to further analyse the effect of rectal evacuatory dysfunction. The analysis included 102 patients who had sham treatment in the CONFIDeNT trial. Results can be seen in Table 29.

Table 29: Univariate logistic regression analysis of sham group in CONFIDeNT Trial

Symptom		**N (%)**	**Success n (%)**	**Failure n (%)**	**p-value**	**Odds ratio**	**Lower 95% CI**	**Upper 95% CI**
Rectal evacuatory difficulties	Present	58 (56.9)	24 (75.0)	34 (48.6)	0.15	3.18	1.26	8.03
	Absent	44 (43.1)	8 (25.0)	36 (51.4)				

Although the odds of 'success' with sham were not statistically significant, the presence of rectal evacuatory difficulty confers a high odds ratio (over 3) of response to sham electrical stimulation. Taken together with the negative effect in the active treatment arm, the reporting of rectal evacuatory difficulty is predictive both of a poor outcome to PTNS and a good outcome to sham electrical stimulation.

This finding reasonably prompts a re-analysis of the CONFIDeNT Trial results, excluding all patients with significant rectal evacuatory problems. Results of the re-analysis of the primary outcome are shown in Table 30.

Table 30: Re-analysis of CONFIDeNT trial data excluding patients with significant rectal evacuatory difficulty: Results of primary outcome

	PTNS, n=47	**Sham, n=44**	**p-value**
≥50% reduction weekly FIE	23 (48.9%)	8 (18.2%)	<0.01
≥25% reduction weekly FIE	30 (57.7%)	14 (31.8%)	<0.01
≥75% reduction weekly FIE	18 (38.3%)	5 (11.4%)	<0.01
100% reduction weekly FIE	8 (17.0%)	2 (4.5%)	0.06

Re-analysis of the results excluding patients with any rectal evacuatory difficulties demonstrates almost 50% of patients had successful treatment with PTNS compared to 18% with sham electrical stimulation. When compared to the 38% success rate with PTNS vs. 31% success rate with sham in the main CONFIDeNT Study, these results are clearly very different. Re-analysis of the categorical reductions using the ≥25%, ≥75% and 100% reduction cut-offs yields similar results (Table 30). Post hoc chi squared testing of these outcomes has been added to the table acknowledging the post hoc nature of such analyses and the fact that these were not adjusted as in the primary CONFIDeNT analysis.

Further analysis of other secondary outcomes, including reduction in mean total weekly FIE, mean weekly urge FIE, mean weekly passive FIE and SMCS are shown in Table 31.

Table 31: Re-analysis of CONFIDeNT trial data excluding patients with significant rectal evacuatory difficulty: Results of secondary outcomes

	PTNS			Sham		
	Baseline	**14 weeks**	**p-value**	**Baseline**	**14 weeks**	**P-value**
Total FIE/wk	5.0 (1.6 – 14.0)	2.0 (0.5 – 5.5)	<0.001	7.3 (2.2 – 16.3)	7.0 (2.0 – 16.4)	0.82
	9.3 (10.4)	4.2 (5.4)		10.9 (12.4)	11.2 (11.6)	
Urge FIE/wk	3.0 (1.0 – 5.5)	1.1 (0.0 – 3.0)	<0.001	2.8 (0.0 – 7.0)	1.5 (0.5 – 11.8)	0.41
	4.7 (5.9)	2.1 (2.8)		5.2 (7.4)	6.2 (8.2)	
Passive FIE /wk	2.0 (0.01-7.5)	0.0 (0.0 – 4.0)	<0.001	2.3 (0.0 – 8.3)	2.5 (0.5 – 8.8)	0.68
	4.6 (5.8)	2.1 (3.2)		5.6 (7.6)	5.1 (6.0)	
SMCS	14.0 (12.0 – 17.0)	14.0 (11.0 – 17.0)	0.82	16.0 (13.3 – 18.0)	15.0 (10.0 – 18.0)	0.12
	14.2 (4.0)	13.8 (4.0)		15.4 (3.8)	14.5 (4.6)	

There was a significant reduction in mean total weekly FIE, mean weekly urge FIE, and mean weekly passive FIE after PTNS treatment, but not after sham treatment. There was however still no significant reduction in mean SMCS in either treatment group.

5.4.3 Limitations of these findings

One limitation to performing logistic regression analysis to predict the patients in whom a successful outcome may be more likely is the small sample size and resulting underpowered statistical analysis. Whilst the sample size calculation performed in the CONFIDeNT Study ensured the main trial was adequately powered, far fewer patients were included in the logistic regression analysis. Interpretation of the results must therefore be viewed in context i.e. that this is in effect a selective post hoc analysis of a study designed with a different hypothesis.

5.4.4 Implications of these findings

The implications of these findings merit some discussion in the context of the primary study results but do not invalidate CONFIDeNT, the results of which remain applicable in the population studied. While noting the limitations, it must still be acknowledged that the analyses performed, based on reasonable a priori hypotheses do yield a single clear and very important result. This is, put simply, that re-analysis of the subgroup of patients who have pure FI with no difficulty in rectal evacuation completely changes the interpretation of the CONFIDeNT trial outcomes. This has important potential implications on the future of the therapy, since if these patients were carefully selected it might be deemed premature to withdraw patient access to PTNS for all patients on the basis of the findings of the CONFIDeNT Trial.

The only way to definitively confirm this association would be to perform a further trial of PTNS in the treatment of patients with FI, in which all patients with any form of rectal evacuatory dysfunction were excluded either on formal symptom evaluation or perhaps on objective radio-physiological testing, or a stratified medicine design was adopted where the presence of RED was a primary stratum for therapy direction. This finding might also affect the design of all further trials of neuromodulation in the treatment of FI in that patients with a significant problem with rectal evacuation should perhaps be excluded. Of note, in the SaFaRI trial, a randomised trial comparing SNS with FENIX magnetic sphincter augmentation for FI, patients with significant obstructed defaecation, defined as an inability to satisfactorily evacuate the rectum and an Obstructed Defaecation Score (ODS)>8, are excluded. Though this trial design was to avoid risks associated with one of the treatments (Fenix, Shoreview, MN, USA) this will likely make for a more clinically relevant trial outcome.

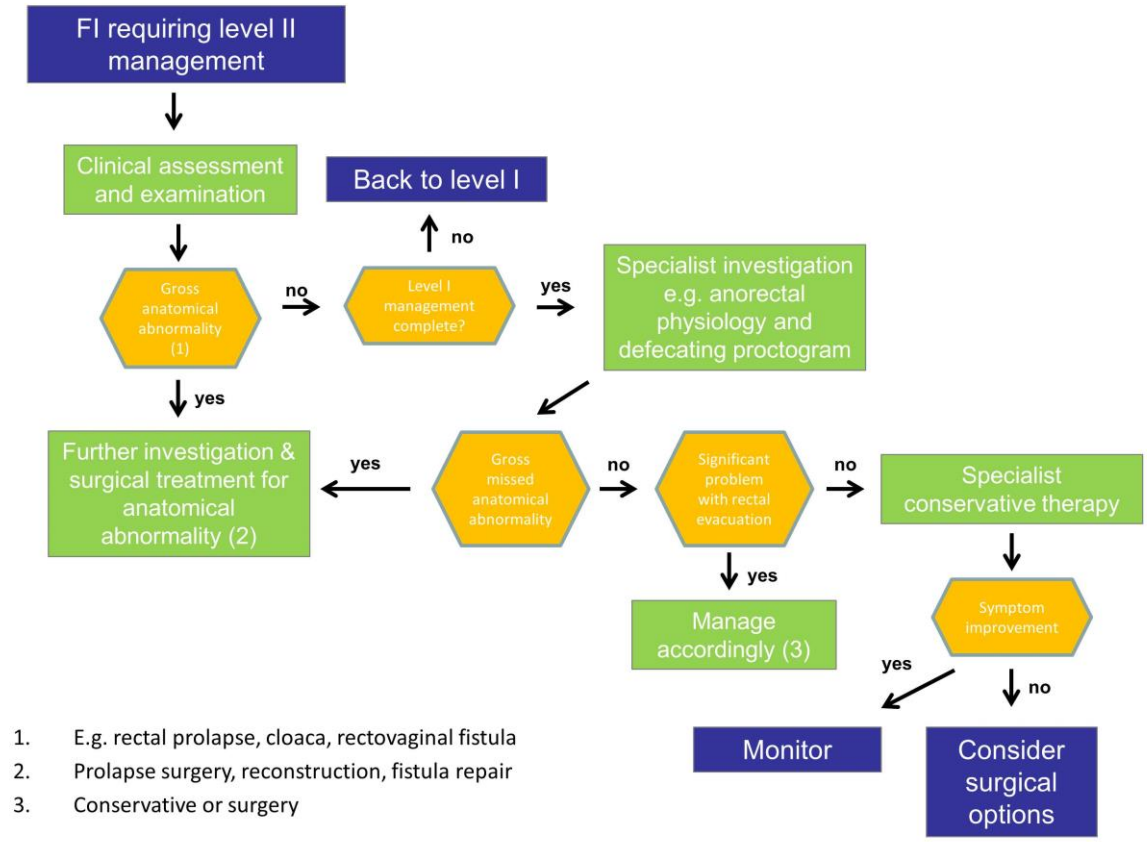
It seems that rectal evacuatory problems are not only a predictor of a negative outcome with PTNS in the treatment of FI, but they are a factor for improved outcomes with

sham stimulation. The presence of rectal evacuatory problems seems to increase the placebo effect, and this finding alone has very important implications for the understanding of the placebo effect and for the future of trials not only in FI but also in rectal evacuatory dysfunction and maybe constipation as a symptom in general.

These findings throw into sharp focus the fact that FI represents a symptom and not a disease. The 'traditional' way of considering FI is to categorise symptoms into predominant passive incontinence, urge incontinence or both. What may, however, be more useful is to consider whether the FI occurs in the presence or absence of a significant problem with rectal evacuation.

At this point, I make reference back to the original algorithm of care for patients with FI shown in Chapter 1.8. Level II (Figure 22**).** This algorithm highlights the importance of excluding any form of rectal evacuatory problem prior to embarking on any surgical procedure for FI.

Figure 22: Algorithm for the treatment of FI



What is unclear is the reason that these two problems often co-exist. One explanation for patients suffering concomitant FI and RED is that overflow FI is a secondary symptom. This has been reported as a common phenomenon in the geriatric and paediatric literature [293], and more recently this finding has also been documented in men [294]. Indeed, this may be due to severe constipation causing faecal impaction, may be secondary to a structural abnormality (e.g. rectocoele or intussusception) or a functional problem of rectal emptying (e.g. paradoxical contraction or inadequate relaxation of the pelvic floor muscles during attempted defaecation and/or inadequate propulsive forces during attempted defaecation). Alternatively, it may be that there is an over-arching pathophysiology encompassing the whole pelvic floor, resulting in a symptom array which manifests in some patients as predominantly FI and some as

predominantly RED, but with all patients suffering symptoms of both. It seems logical, therefore, that whilst all patients present with FI, those with significant problems with rectal evacuation may represent a very different disease process and to expect a treatment such as PTNS to successfully treat both is ambitious. It is likely that patients who suffer with isolated FI require a different management strategy than those with concomitant FI and rectal evacuatory dysfunction.

It would have been very interesting to have performed anorectal physiology studies including a defaecating proctogram on all patients in the CONFIDeNT Trial, in order to further categorise their rectal evacuatory dysfunction. Unfortunately, due to factors of available expertise and cost, this step was not included in the protocol.

5.4.5 Conclusion

In conclusion, the only predictor of PTNS outcome for FI as determined at 14 weeks is the presence of any form of rectal evacuatory difficulty, which confers a statistically significant negative effect. For the interpretation of CONFIDeNT, this finding is compounded by the positive effect that this explanatory covariate has on outcome from sham electrical stimulation. Taken together there is strong motivation to revisit the efficacy / effectiveness evaluation of PTNS based on a starting cohort that excludes such patients.

6 The CONFIDeNT Follow-up Study

6.1 Introduction

The aim of the CONFIDeNT Study was to ascertain efficacy of PTNS vs. sham stimulation in the treatment of patients with FI. Whilst this study is pivotal in ascertaining the short-term efficacy of PTNS, it does not examine the long-term results for these patients. Following up all patients for 1-year after completion of the CONFIDeNT Study, would provide useful data regarding the ongoing efficacy of PTNS and the efficacy of PTNS in those patients who initially had sham in the trial. It would also inform requirement and timing of top-up treatments, effects on quality of life, acceptability of PTNS and requirement for further treatments.

6.1.1 Study Aims

The aim of this 1-year observational study was to follow up all CONFIDeNT Trial patients, including PTNS and sham arms, at 6 months and 1 year, to inform about:

- long-term effectiveness of PTNS in those who had successful treatment
- requirement for and timing of 'top-up' treatments in those with initial treatment success
- outcome of sham patients: including both sham successes and sham failures
- requirement of other treatments following unsuccessful PTNS or following the treatment effect subsiding

6.2 Methods

6.2.1 Overview: Study Design

The CONFIDeNT Follow-up Study was a 1-year observational study, conducted by the lead centre of the CONFIDeNT Trial, Queen Mary University London. All patients who completed the CONFIDeNT Trial were followed up at 6 months and 1 year following their PTNS or sham treatment by post and telephone.

6.2.2 Study outcomes

Clinical outcomes:

Outcomes were assessed at two time-points, 6 months and 1 year following PTNS or sham treatment in the CONFIDeNT Trial. Clinical outcomes were derived from 1-week bowel diaries and investigator-administered questionnaires.

Primary outcome:

The pragmatic primary outcome of this study is binary i.e. continued success or failure, with treatment success defined as achieving ≥ 50% reduction in total FI episodes per week.

Secondary outcomes:

- Change in total FI episodes per week as a continuous measure;
- Change in urge FI episodes per week as a continuous measure;
- Change in passive FI episodes per week as a continuous measure;
- Change in symptom severity score: St Mark's Continence Score (SMCS). A score from 0 (best) -24 (worst) with >5 indicating significant symptoms [252];
- Likert scale of patients global impression of success (scale 0-10);
- Length of effectiveness of PTNS

- Requirement and timing of PTNS 'top-up' treatments
- Requirement for other treatments or surgery for FI
- Qualitative data:
    - Patient perceived impression of change in use of incontinence pads and constipating medications;
    - Patient perceived impression of change in urinary symptoms;

6.2.3 Plan of analysis

Analyses were performed comparing data collected at baseline and after the CONFIDenT Trial with those collected in the follow-up study i.e. 6 months and 1 year following the CONFIDeNT Trial. Analysis was performed on three separate groups:

- Group 1: Patients who had PTNS in the CONFIDeNT Trial
- Group 2: Patients who had PTNS either in the CONFIDeNT Trial or following sham in the CONFIDeNT Trial
- Group 3: All patients in the follow-up study

Analysis was conducted using IBM SPSS Statistics Version 21. All data are presented as descriptive statistics, with no formal statistical analysis between groups.

6.2.4 Study population

All patients who completed the CONFIDeNT Trial were eligible for inclusion into the follow-up study. Since ethical approval for this study was granted after the CONFIDeNT Trial, only patients who were finishing treatment on or after 1st October 2012, or those who were contacted subsequently, were included. The inclusion and exclusion criteria were otherwise the same as for the CONFIDeNT Trial.

6.2.5 Data collection

Each eligible patient from the CONFIDeNT Study was approached to seek agreement for enrolment in the CONFIDeNT follow-up study. Events were as follows:

Visit 13 CONFIDeNT Study: Patients were invited to be involved in the follow-up study and given a Patient Information Sheet at this visit if interested.

Visit 14 CONFIDeNT Study: At Visit 14, two weeks later, patients were consented for the follow-up study, and their details passed on securely to the lead centre where the follow-up study was co-ordinated.

6-months following CONFIDeNT Study completion: Patients were contacted by telephone to complete the questionnaires, and were posted a 1-week bowel diary, which was returned in a stamped, addressed envelope.

12-months following CONFIDeNT Study completion: Patients were again contacted by telephone to complete the questionnaires, and were posted a 1-week bowel diary, which was returned in a stamped, addressed envelope.

6.2.6 Loss to follow-up

Three attempts were made to contact each patient at 6-months and 1-year by telephone and post or email. If these were unsuccessful, the patients were presumed lost to follow-up.

6.2.7 Withdrawal from study

If patients wished to withdraw from the follow-up study, they were free to do so at any time without giving a reason.

6.2.8 Ethical arrangements and research governance

This trial was granted ethical approval in October 2012 (REC Reference: 10/H0703/25- Substantial Amendment 4). The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments. The trial was compliant with the approved protocol and REC conditions of approval, and in line with Good Clinical Practice Guidelines.

6.2.9 Trial oversight

The trial was under the auspices of the Chief Investigator and was sponsored by Queen Mary University London. It was funded by the Chief Investigator's department through a donation from Uroplasty.

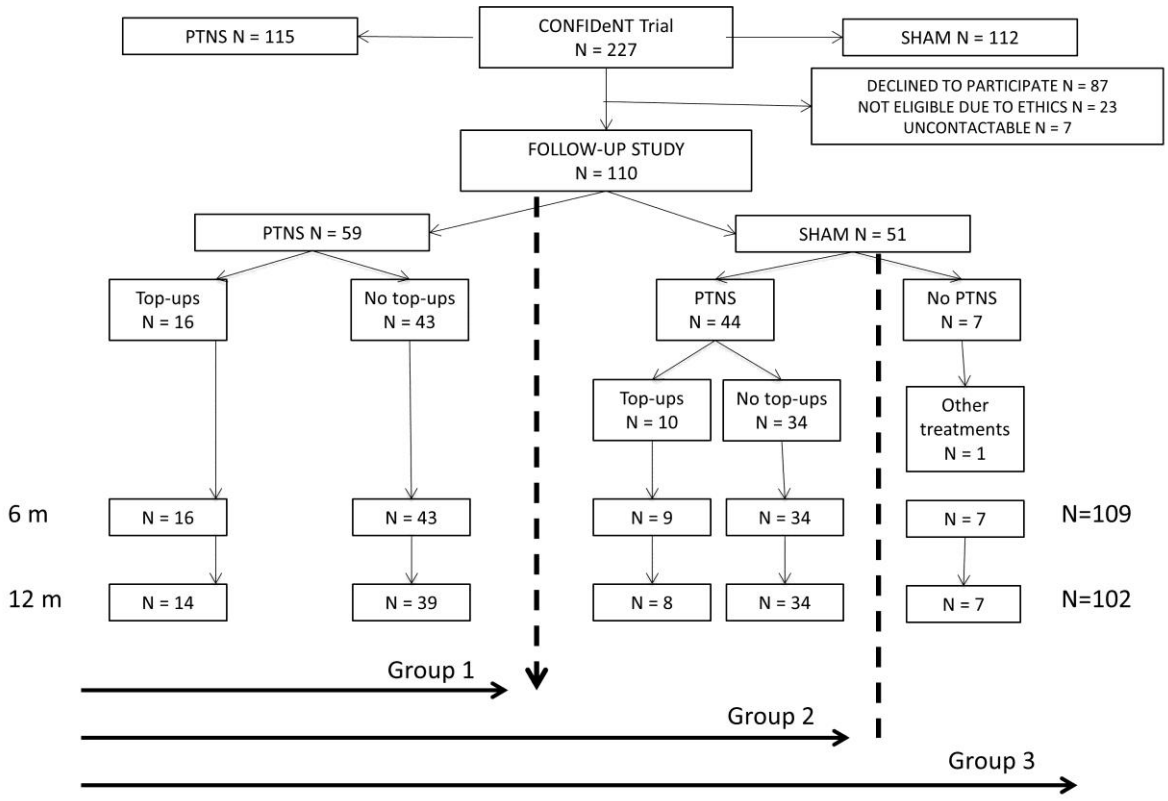
The project was overseen by a Trial Steering Committee (TSC). The TSC included an independent chair, and met 6 monthly throughout to provide overall supervision and ensure the trial was conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice.

6.3 Results

6.3.1 Patient flow

The flow of patients through the trial is shown in the CONSORT diagram below (Figure 23). This figure also demonstrates the three groups in which analysis of the CONFIDeNT Follow-up study was performed. Group 1 included patients who had PTNS in the CONFIDeNT Study; Group 2 included patients who either had PTNS in the CONFIDeNT Study or had PTNS following sham in the CONFIDeNT Study; Group 3 included all patients in the CONFIDeNT Follow-up study (i.e. also including those patients who had sham in the CONFIDeNT Study but did not go on to have PTNS afterwards). Inclusion of Group 3 was justified to avoid reporting bias.

Figure 23: CONSORT diagram for CONFIDeNT Follow-up Study



6.3.2 Trial recruitment

110 patients from 12 centres were recruited to the study between 1st October 2012 and 23rd February 2014. The trial centres were: Barts Health NHS Trust, London; Aintree University Hospital, Liverpool; University Hospital Southampton NHS Foundation Trust; Sandwell General Hospital, Birmingham; Sheffield Teaching Hospital; Ching Way Medical Centre, London; Queen's Medical Centre, Nottingham; Castle Hill Hospital, Hull; University College Hospital, London; St Thomas' Hospital, London; Pilgrim Hospital, Lincolnshire; University Hospital of South Manchester. The number of patients per centre ranged from 1 to 22. Of the 117 patients who did not enrol on the CONFIDeNT Follow-up study, 23 were not eligible since ethical approval for this study had not yet been granted, 7 were un-contactable, and the remaining 87 were either not approached for participation or did not consent. At 6 months, 109 patients were available for follow-up (one patient was un-contactable at 6 months), and at 12 months, 102 patients were available for follow-up. Between the 6 month and 1 year time point 6 patients were lost to follow-up.

6.3.3 Data return

A bowel diary was returned at 6 months by 75 (68%) patients and at 12 months by 69 (63%) patients. Questionnaires were completed at 6 months by 109 (99%) patients and at 12 months by 102 (93%) patients.

6.3.4 Patient demographics and clinical data

Demographic data for the three groups analysed in the CONFIDeNT Follow-up Study can be seen in Table 32. In all groups 93% of the patients were female and the median age was 57 years. This corresponds with baseline data from the CONFIDeNT Study. Mean symptom duration was 115.9 months (S.D. 122.3), and this corresponds with baseline data from the CONFIDeNT Study. Demographics of the three groups were similar in terms of obstetric history, bowel function history, bladder function history

and previous treatments for FI, and this was similar to the baseline demographic data of all CONFIDeNT Study patients.

Table 32: Baseline demographic and clinical data of CONFIDeNT Follow up study

	All CONFIDeNT patients	**Group 1**	**Group 2**	**Group 3**
N	**227**	**59**	**103**	**110**
Sex (female)	205 (90%)	55 (93.2%)	96 (93.2%)	103 (93.6%)
Age (years)	57.2 (12.2) 58.0 (49.0, 66.0)	57.4 (11.1) 57.0 (49.0 – 67)	57.2 (10.4) 57.0 (50.0 – 66.0)	56.6 (11.1) 57 (49.0 – 65.3)
Duration of symptoms (months)	96.3 (105.2) 58.0 (49.0, 66.0)	129.8 (130.3) 72.0 (36.0 – 186.0)	119.4 (125.5) 68.0 (36.0 – 177.0)	115.9 (122.3) 64.0 (36.0 – 168.0)
6 month follow-up	NA	6.5 (0.9) 6.4 (5.8 – 7.0)	6.6 (1.0) 6.5 (6.0 – 7.4)	6.6 (1.0) 6.5 (6.1 – 7.4)
12 month follow up	NA	12.5 (0.7) 12.4 (12.0 – 12.9)	12.5 (0.7) 12.3 (12.0 – 12.9)	12.5 (0.7) 12.4 (12.0 – 13.0)
Obstetric history				
Parous*	191 (93%)	49 (89.1%)	87 (90.6%)	94 (91.3%)
Vaginal deliveries only*	186 (97%)	46 (93.9%)	84 (96.6%)	91 (96.8%)
Caesarean sections only*	5 (3%)	3 (6.1%)	3 (3.4%)	3 (3.2%)
Episiotomies or tears*	160 (86%)	41 (74.5%)	73 (83.9%)	78 (85.7%)
Faecal incontinence history				
Passive FI	174 (77%)	44 (74.6%)	71 (68.9%)	77 (70%)
Urge FI	187 (82%)	51 (86.4%)	88 (85.4%)	93 (84.5%)
Flatus incontinence	157 (69%)	35 (59.3%)	63 (61.2%)	70 (63.6%)
Evacuatory difficulties	93 (41%)	25 (42.4%)	46 (44.7%)	51 (46.4%)
Straining	71 (31%)	20 (33.9%)	36 (35%)	37 (36.6%)
Digitation	27 (12%)	7 (11.9%)	14 (13.6%)	15 (13.6%)
Urinary symptom history				
Urinary symptoms	142 (63%)	45 (76.3%)	74 (71.8%)	79 (71.8%)
Urinary urgency	99 (44%)	30 (50.8%)	49 (47.6%)	53 (48.2%)
Urinary urge incontinence	81 (36%)	26 (44.1%)	45 (43.7%)	49 (44.5%)

*females only

6.3.5 Analysis for Group 1

At 6 months, Group 1 comprised 59 patients, which reduced to 53 patients by 12 months. Median time to 6 month follow-up was 6.5 months (IQR 5.8 – 7.0). Median time to 12 month follow-up was 12.4 (IQR 12.0 – 12.9) months.

6.3.5.1 Primary outcome

In those patients in whom it could be calculated (the subset who completed bowel diaries), the percentage of patients achieving treatment success at 6 and 12 months follow up, according to the primary outcome (at least a 50% reduction in weekly FIE) was slightly higher than the percentage that achieved this outcome directly after the CONFIDeNT Trial (42.1% after CONFIDeNT Trial vs. 54.3% at 6 months and 54.8% at 12 months) (Table 33).

Table 33: Primary outcomes for CONFIDeNT Follow-up Study – Group 1

	14 weeks	**6 months**	**12 months**
N	**N = 57**	**N = 37**	**N=31**
≥ 50% reduction in FIE, n (%)	24 (42.1%)	19 (54.3%)	17 (54.8%)
≥25% reduction in FIE, n (%)	27 (47.4%)	25 (67.6%)	19 (61.3%)
≥75% reduction in FIE, n (%)	17 (29.8%)	16 (43.2%)	15 (48.4%)
100% reduction in FIE, n (%)	7 (12.3%)	14 (37.8%)	9 (29.0%)

6.3.5.2 Secondary outcomes

The proportion of patients who achieved a ≥25%, ≥75% and 100% reduction in weekly FIE was also higher at 6 and 12 months than after the CONFIDeNT Trial. The proportion of patients achieving a ≥25% reduction in weekly FIE rose by 20% from after the CONFIDeNT Trial to 6 months (47.4% vs. 67.6%), which was sustained at 12 months (61.3%). The increase in the proportion of patients achieving a ≥75% reduction in weekly FIE was not so marked, however the proportion of patients who

achieved a 100% reduction in weekly FIE was three times higher at 6 months than after the CONFIDeNT Trial (37.8% vs 12.3%).

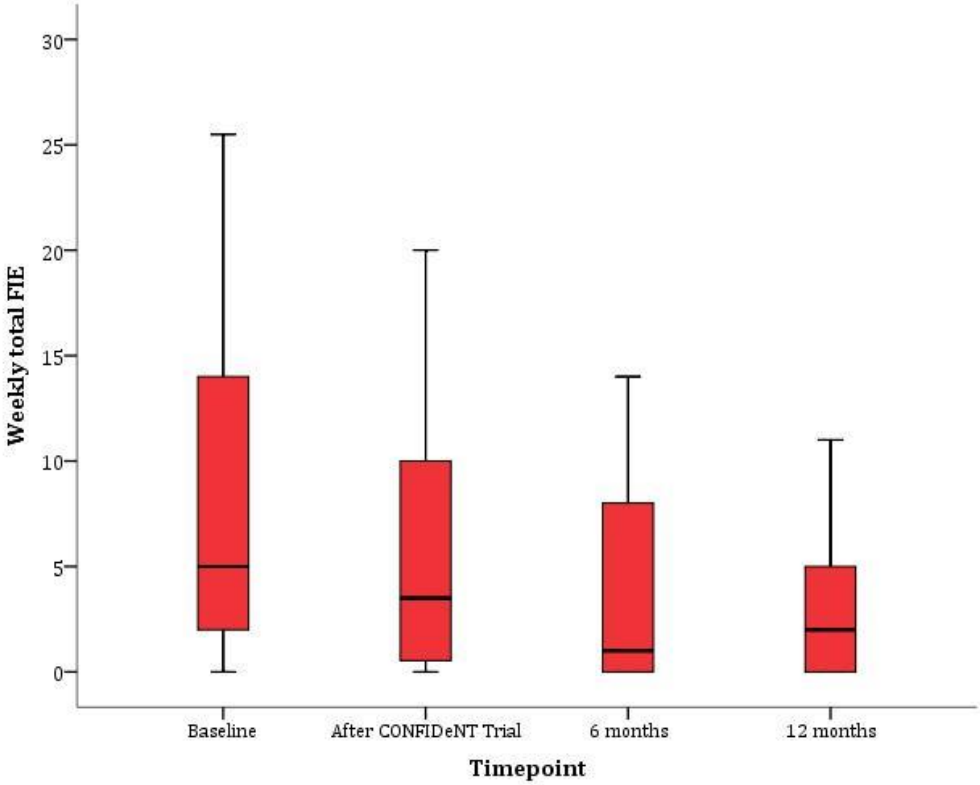
The weekly total FIE at baseline, after the CONFIDeNT Study and at 6 and 12 months follow-up can be seen in Table 34 and Figure 24. In Group 1, the reduction in weekly total FIE after the CONFIDeNT Trial was sustained at 6 and 12 months follow-up.

Urge faecal incontinence episodes and passive faecal incontinence episodes at baseline, after the CONFIDeNT Study and at 6 and 12 months follow up can be seen in Table 34, Figure 25 and Figure 26. The initial reduction in mean weekly urge and passive FIE after the CONFIDeNT Trial was sustained at 6 months or 12 months follow-up.

Table 34: Secondary outcomes for CONFIDeNT Follow-up Study – Group 1

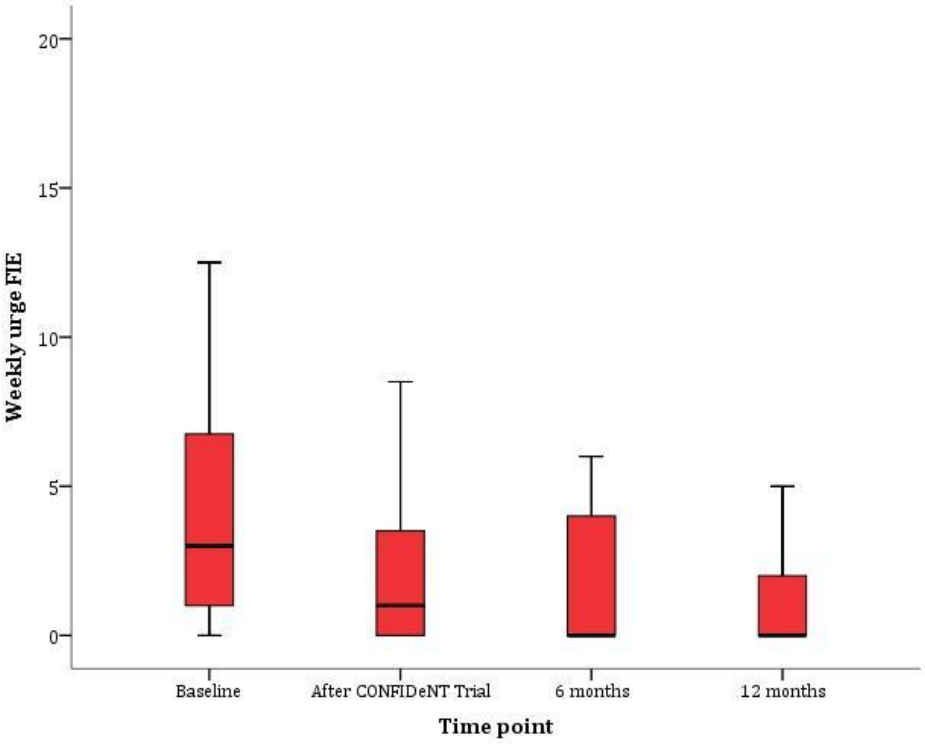
	Baseline	**14 weeks**	**6 months**	**12 months**
Bowel diary data				
N	N = 58	N = 58	N = 37	N=33
FI episodes/week *[median (interquartile range)]*	5.0 (1.9 – 14.0)	3.5 (0.53 – 10.0)	1.0 (0.0 – 8.5)	2.0 (0.0 – 5.0)
[mean (standard deviation)]	9.3 (10.8)	6.3 (7.8)	5.8 (10.1)	5.6 (14.1)
Urge FI episodes/week	3.0 (1.0 – 7.5)	1.0 (0.0 – 4.0)	0.0 (0.0 – 4.0)	0.0 (0.0 – 3.0)
	4.5 (5.4)	3.2 (4.5)	3.4 (6.3)	2.8 (7.2)
Passive FI episodes/week	1.5 (0.0 – 8.1)	1.8 (0.0 – 4.9)	0.0 (0.0 – 3.0)	0.0 (0.0 – 3.5)
	4.8 (6.3)	3.1 (4.1)	2.5 (5.0)	2.8 (7.7)
St. Mark's Continence Score (0 [best]-24 [worst])				
N	N = 57	N = 54	N = 59	N=53
Median (IQR) and mean (SD)	15.0 (12.5 – 17.0)	14.0 (11.8 – 17.0)	11.0 (7.0 – 13.0)	12.0 (6.5-14.0)
	14.9 (3.5)	14.1 (4.0)	10.6 (3.9)	10.4 (4.6)
SMCS >5	57 (100%)	54 (100%)	55 (93.2%)	38 (71.7%)

Figure 24: CONFIDeNT Follow-up Study: Weekly total FIE: Group 1



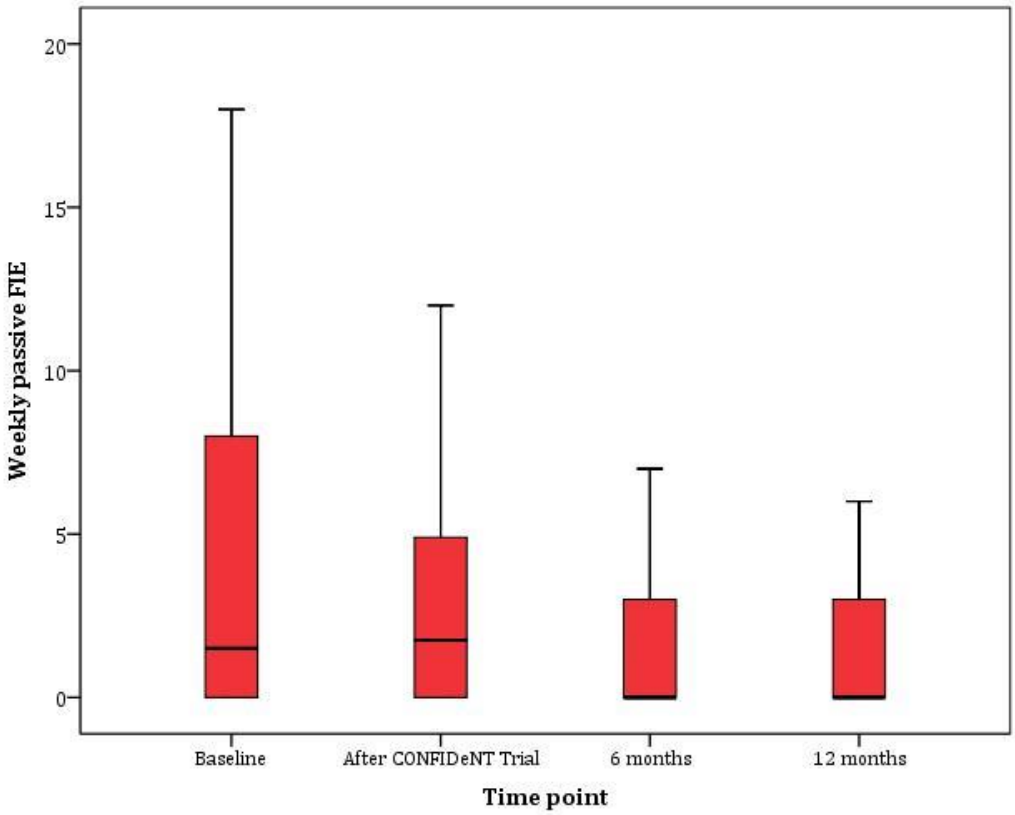
**Baseline: n=58; After CONFIDeNT Trial: n=58; 6 months: n=37; 12 months: n=33*

Figure 25: CONFIDeNT Follow-up Study: Weekly urge FIE: Group 1



**Baseline: n=59; After CONFIDeNT Trial: n=58; 6 months: n=37; 12 months: n=33*

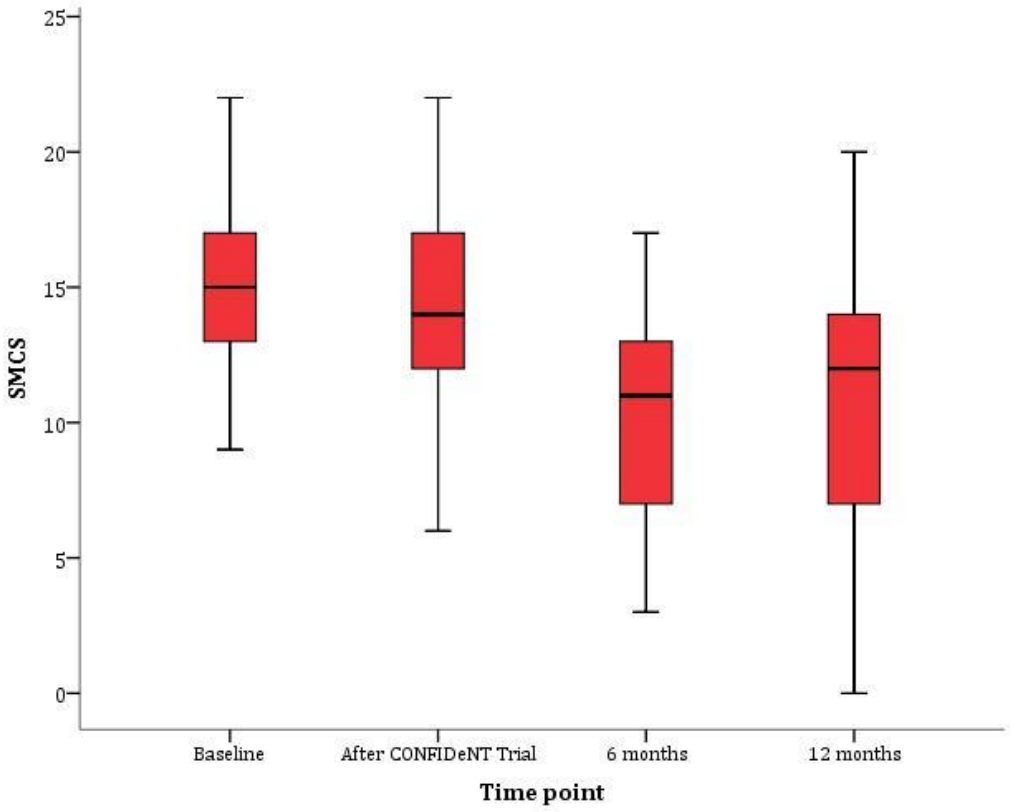
Figure 26: CONFIDeNT Follow-up Study: Weekly passive FIE: Group 1



**Baseline: n=59; After CONFIDeNT Trial: n=58; 6 months: n=37; 12 months: n=33*

The SMCS at baseline, after the CONFIDeNT Study and at 6 months and 12 months follow up can be seen in Table 34 and Figure 27. Though there was not a significant reduction in SMCS after the CONFIDeNT Trial, there was a 4 point reduction in SMCS at both 6 month and 12 month follow-up.

Figure 27: CONFIDeNT Follow-up Study: SMCS: Group 1



**Baseline: n=57; After CONFIDeNT Trial: n=54; 6 months: n=59; 12 months: n=53*

6.3.6 Analysis for Group 2

At 6 months, Group 2 comprised 103 patients, which reduced to 95 patients at 12 months. Median time to 6 month follow-up was 6.5 months (IQR 6.0 – 7.4). Median time to 12 month follow-up was 12.3 (IQR 12.0 – 12.9) months.

6.3.6.1 Primary outcome

The percentage of patients achieving treatment success at 6 and 12 months follow up, according to the primary outcome (at least a 50% reduction in weekly FIE) was similar to the percentage that achieved this outcome directly after the CONFIDeNT Trial (35.6% after CONFIDeNT Trial vs. 40.3% at 6 months and 44.3% at 12 months) (Table 35).

Table 35: Primary outcomes for CONFIDeNT Follow-up Study – Group 2

	After CONFIDeNT	6 months	12 months
N	**N = 101**	**N = 72**	**N=61**
≥ 50% reduction in FIE, n (%)	36 (35.6%)	29 (40.3%)	27 (44.3%)
≥25% reduction in FIE, n (%)	44 (43.6%)	38 (52.8%)	33 (54.1%)
≥75% reduction in FIE, n (%)	9 (18.8%)	23 (31.9%)	22 (36.1%)
100% reduction in FIE, n (%)	8 (7.9%)	20 (27.8%)	13 (21.3%)

6.3.6.2 Secondary outcomes

The proportion of patients who achieved ≥25% and ≥75% reductions in weekly FIE increased from after the CONFIDeNT Trial to 6 months and again to 12 months. This increase was more marked in the ≥75% outcome and the ≥100% outcome, with almost three times the number of patients achieving this outcome at 12 months compared to after the CONFIDeNT Trial.

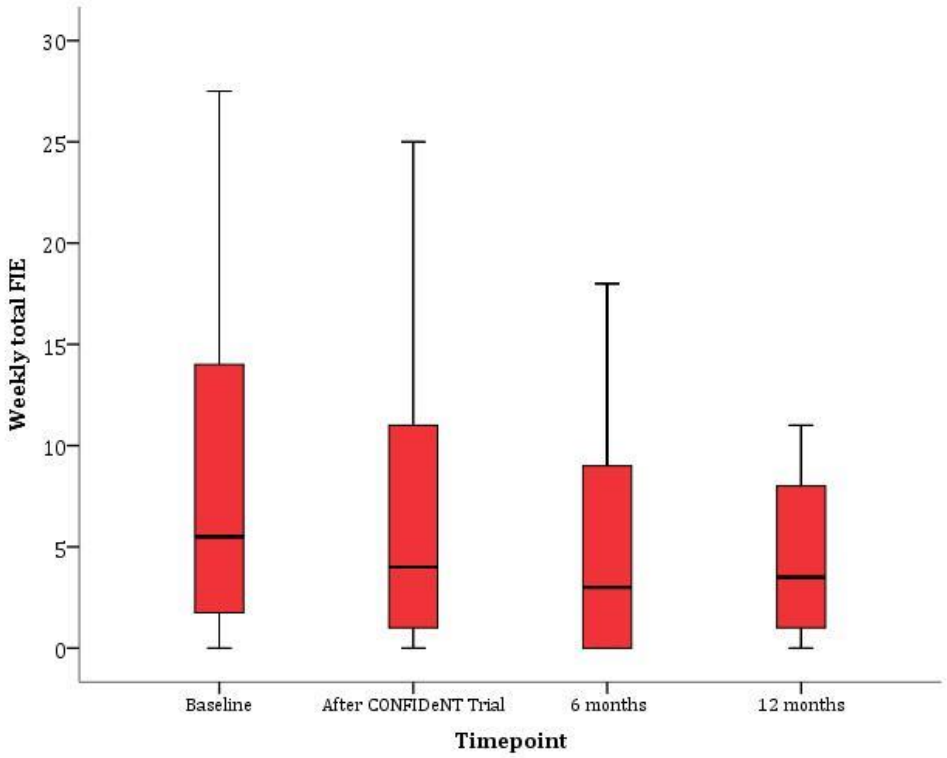
The weekly total FIE at baseline, after the CONFIDeNT Study and at 6 and 12 months follow-up can be seen in Table 36 and Figure 28. The reduction in weekly total FIE after the CONFIDeNT Trial was sustained at 6 months and 12 months follow up, compared to baseline.

Urge faecal incontinence episodes and passive faecal incontinence episodes at baseline, after the CONFIDeNT Study and at 6 and 12 months follow-up can be seen in Table 36, Figure 29 and Figure 30. A similar mean weekly number of urge FIE was seen at 6 and 12 months follow-up compared to that after the CONFIDeNT trial. Similar results were seen for mean weekly passive FIE.

Table 36: Secondary outcomes for CONFIDeNT Follow-up Study – Group 2

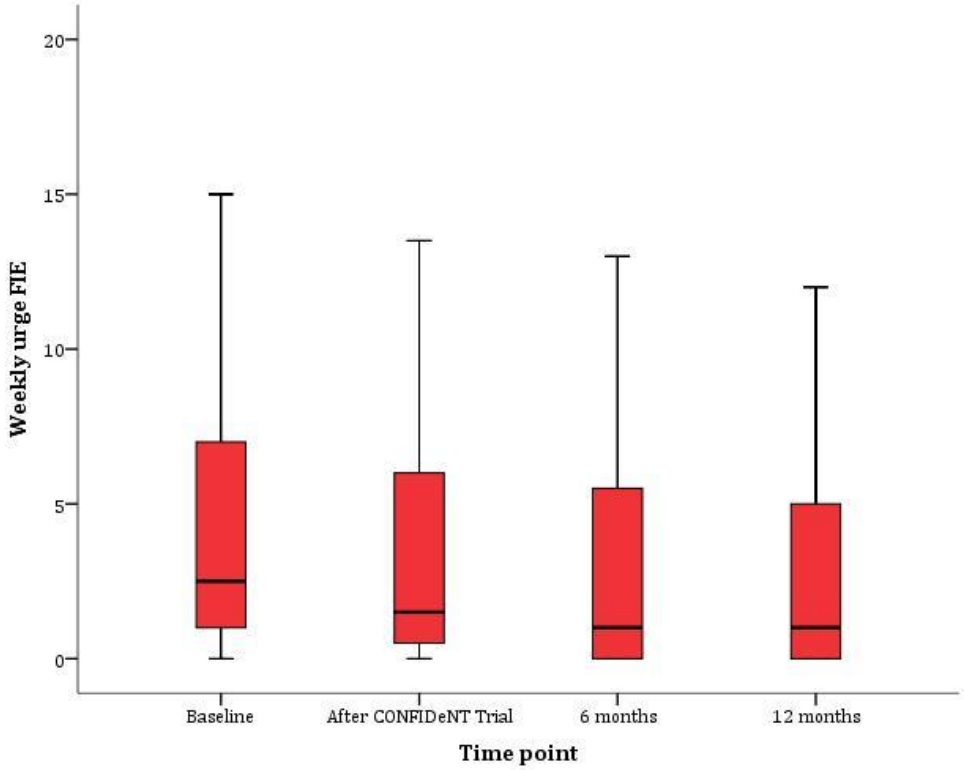
	Baseline	**14 weeks**	**6 months**	**12 months**
Bowel diary data				
	N = 102	**N = 102**	**N = 72**	**N = 66**
FI episodes/week *[median (interquartile range)]*	5.5 (1.7 – 14.0)	4.0 (1.0 – 11.1)	3.0 (0.0 – 9.0)	3.5 (0.8-8.5)
[mean (standard deviation)]	9.4 (10.5)	7.7 (9.3)	8.3 (12.4)	7.8 (13.4)
Urge FI episodes/week	2.5 (1.0 – 7.0)	1.5 (0.5 – 6.0)	1.0 (0.0 – 5.8)	1.0 (0.0-5.0)
	4.6 (5.3)	4.1 (6.0)	4.7 (8.5)	3.8 (7.0)
Passive FI episodes/week	1.5 (0.0 – 7.5)	1.5 (0.0 – 5.5)	0.5 (0.0 – 5.0)	1.0 (0.0-5.0)
	4.7 (7.0)	3.6 (5.5)	3.6 (6.2)	4.0 (7.7)
St. Mark's Continence Score (0 [best]-24 [worst])				
N	**N = 99**	**N = 95**	**N = 102**	**N=95**
Median (IQR) and mean (SD)	16.0 (13.0 – 18.0	15.0 (12.0 – 18.0)	11.0 (8.0 – 13.25)	12.0 (8.0 – 15.0)
	15.5 (3.7)	14.7 (4.1)	10.8 (3.8)	11.2 (4.3)
SMCS >5	99 (100%)	95 (100%)	97 (95.1%)	76 (91.6%)

Figure 28: CONFIDeNT Follow-up Study: Weekly total FIE: Group 2



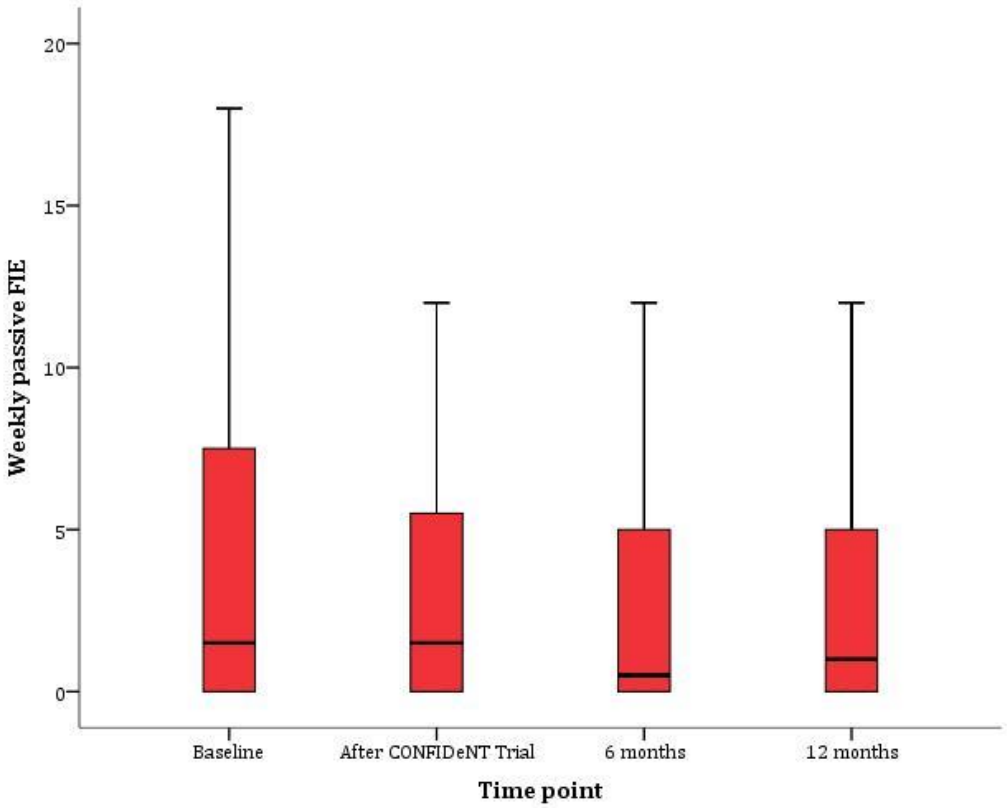
**Baseline: n=102; After CONFIDeNT Trial: n=102; 6 months: n=72; 12 months: n=66*

Figure 29: CONFIDeNT Follow-up Study: Weekly urge FIE: Group 2



**Baseline: n=103; After CONFIDeNT Trial: n=102; 6 months: n=72; 12 months: n=66*

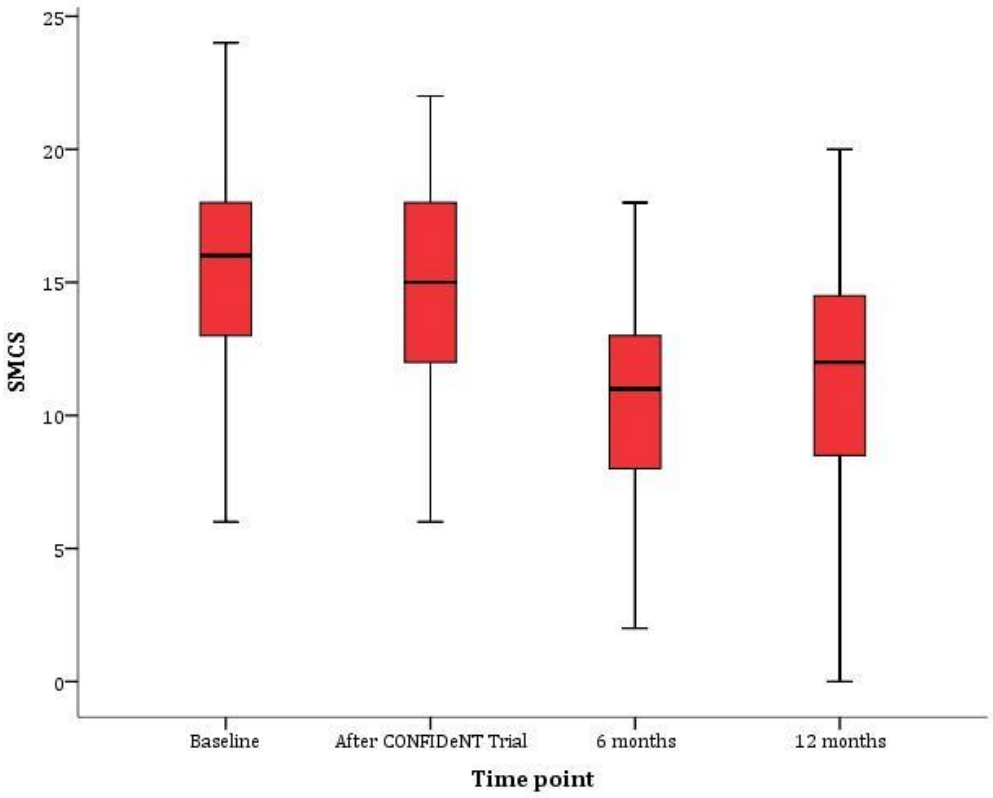
Figure 30: CONFIDeNT Follow-up Study: Weekly passive FIE: Group 2



**Baseline: n=102; After CONFIDeNT Trial: n=102; 6 months: n=72; 12 months: n=66*

The SMCS at baseline, after the CONFIDeNT Study and at 6 months and 12 months follow up can be seen in Table 36 and Figure 31. Though there was not a significant reduction in SMCS after the CONFIDeNT Trial, there was again a 4-point reduction in SMCS at both 6 month and 12 month follow-up.

Figure 31: CONFIDeNT Follow-up Study: SMCS: Group 2



**Baseline: n=99; After CONFIDeNT Trial: n=95; 6 months: n=102; 12 months: n=95*

6.3.7 Analysis for Group 3

At 6 months, this group comprised 109 patients, and at 12 months this reduced to 102 patients. Median time to 6 month follow-up was 6.5 months (IQR 6.1 – 7.4). Median time to 12 month follow-up was 12.4 (IQR 12.0 – 13.0) months.

6.3.7.1 Primary outcome

The percentage of patients achieving treatment success at 6 and 12 months follow up, according to the primary outcome (at least a 50% reduction in weekly FIE) was similar to the percentage that achieved this outcome directly after the CONFIDeNT Trial (37.4% after CONFIDeNT Trial vs. 40.0% at 6 months and 43.8% at 12 months) (Table 37).

Table 37: Primary outcomes for CONFIDeNT Follow-up Study – Group 3

	After CONFIDeNT	6 months	12 months
N	**N = 107**	**N = 75**	**N=64**
≥ 50% reduction in FIE, n (%)	40 (37.4%)	30 (40.0%)	28 (43.8%)
≥25% reduction in FIE, n (%)	49 (45.8%)	39 (52.0%)	34 (53.1%)
≥75% reduction in FIE, n (%)	22 (20.6%)	23 (30.7%)	22 (34.4%)
100% reduction in FIE, n (%)	9 (8.4%)	20 (26.7%)	13 (20.3%)

6.3.7.2 Secondary outcomes

The proportion of patients who achieved ≥25% and ≥75% reductions in weekly FIE increased from after the CONFIDeNT Trial to 6 months and 12 months. This increase was more marked in the ≥75% outcome. The number of patients who achieved 100% reduction in weekly FIE rose from 8.4% after the CONFIDeNT Trial to 26.7% at 6 months, and was 20.3% at 12 months.

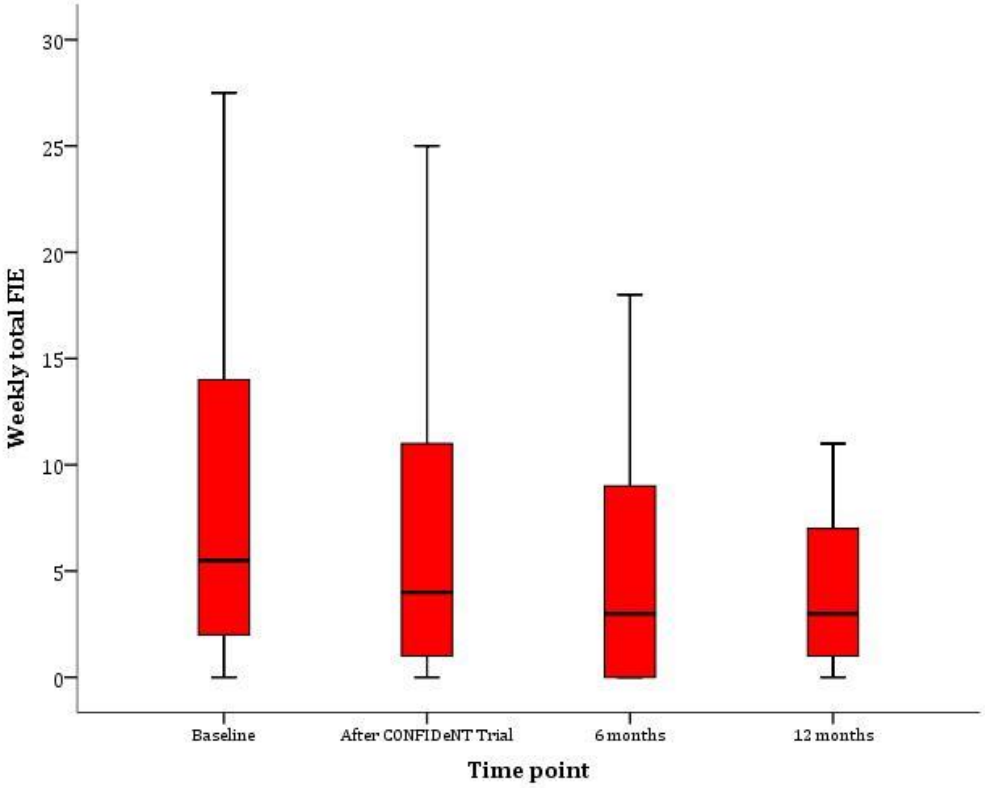
The weekly total FIE at baseline, after the CONFIDeNT Study and at 6 and 12 months follow-up can be seen in Table 38 and Figure 32. There was a significant reduction in total weekly FIE after the CONFIDeNT trial compared to baseline, with similar weekly FIE reported at 6 month and 12 month follow-up. Urge faecal incontinence episodes and passive faecal incontinence episodes at baseline, after the CONFIDeNT Study and at 6 and 12 months follow-up can be seen in Table 38, Figure 33 and Figure 34.

The significant reduction in weekly urge FIE after the CONFIDeNT Trial seemed to be maintained at 6 months and 12 months follow-up. The reduction in passive FIE seen after the CONFIDeNT Trial was also sustained at 6 month and 12 month follow-up.

Table 38: Secondary outcomes for CONFIDeNT Follow-up Study – Group 3

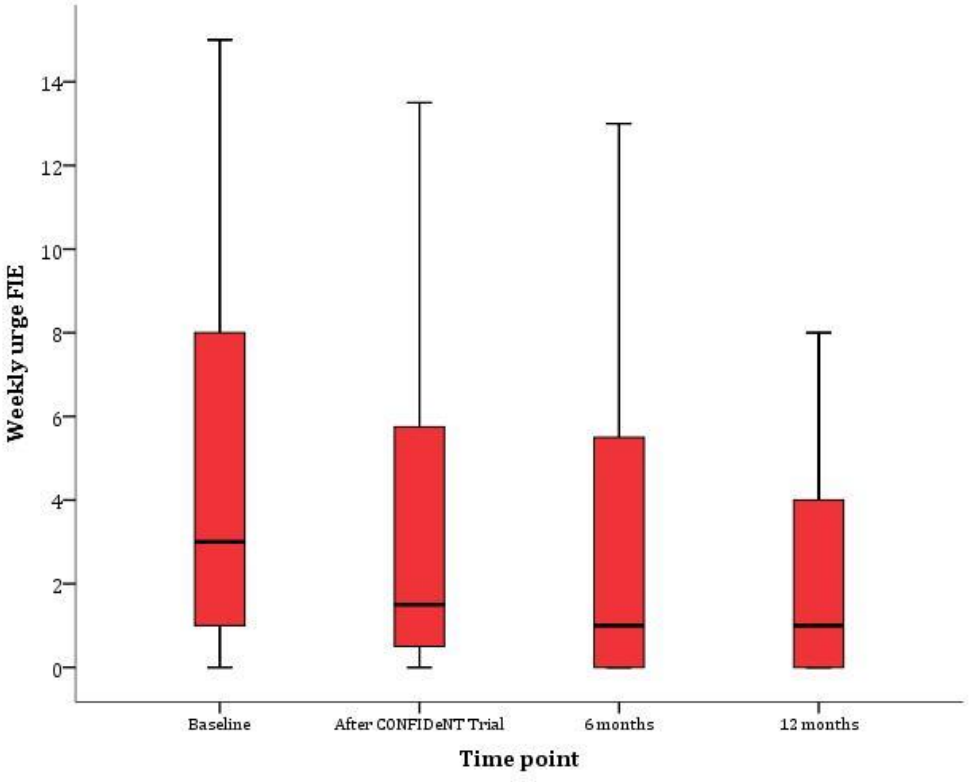
	Baseline	**After CONFIDeNT**	**6 months**	**12 months**
Bowel diary data				
N	**N = 109**	**N = 108**	**N = 75**	**N=69**
FI episodes/week *[median (interquartile range)]*	5.5 (2.0 – 14.25)	4.0 (1.0 – 11.0)	3.0 (0.0 – 9.0)	3.0 (1.0 – 7.5)
[mean (standard deviation)]	10.0 (11.9)	7.8 (9.7)	8.1 (12.1)	7.6 (13.2)
Urge FI episodes/week	3.0 (1.0 – 8.0)	1.5 (0.5 – 5.9)	1.0 (0.0 – 6.0)	1.0 (0.0-4.5)
	5.1 (6.3)	4.2 (6.2)	4.6 (8.4)	3.8 (6.9)
Passive FI episodes/week	1.5 (0.0 – 7.5)	1.5 (0.0 – 5.4)	0.0 (0.0 – 5.0)	1.0 (1.0 – 5.0)
	4.8 (7.2)	3.6 (5.6)	3.5 (6.1)	3.9 (7.5)
St. Mark's Continence Score (0 [best]-24 [worst])				
N	**N = 105**	**N = 102**	**N = 109**	**N=102**
Median (IQR) and mean (SD)	16.0 (13.0 – 16.0)	15.0 (12.0 – 18.0)	11.0 (7.5 – 13.5)	12.0 (8.0 – 15.0)
	15.7 (3.7)	14.7 (4.1)	10.7 (3.8)	11.1 (4.5)
SMCS>5	105 (100%)	102 (100%)	103 (94%)	93 (91%)

Figure 32: CONFIDeNT Follow-up Study: Weekly total FIE: Group 3



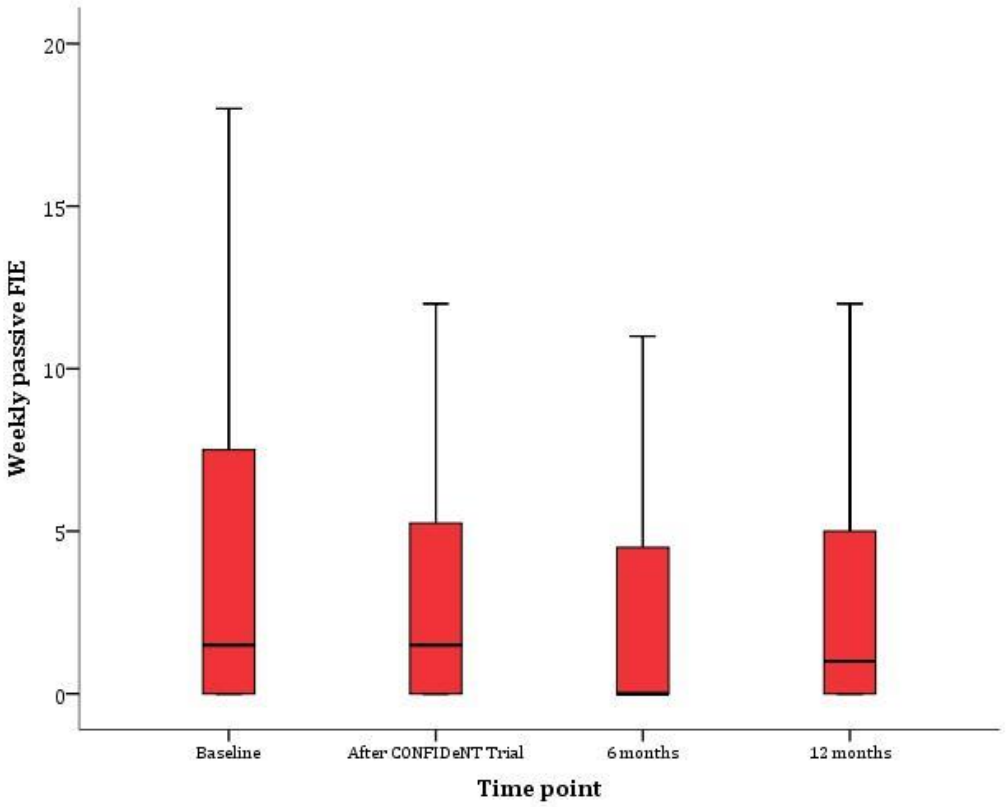
**Baseline: n=109; After CONFIDeNT Trial: n=108; 6 months: n=75; 12 months: n=69*

Figure 33: CONFIDeNT Follow-up Study: Weekly urge FIE: Group 3



**Baseline: n=110; After CONFIDeNT Trial: n=108; 6 months: n=75; 12 months: n=69*

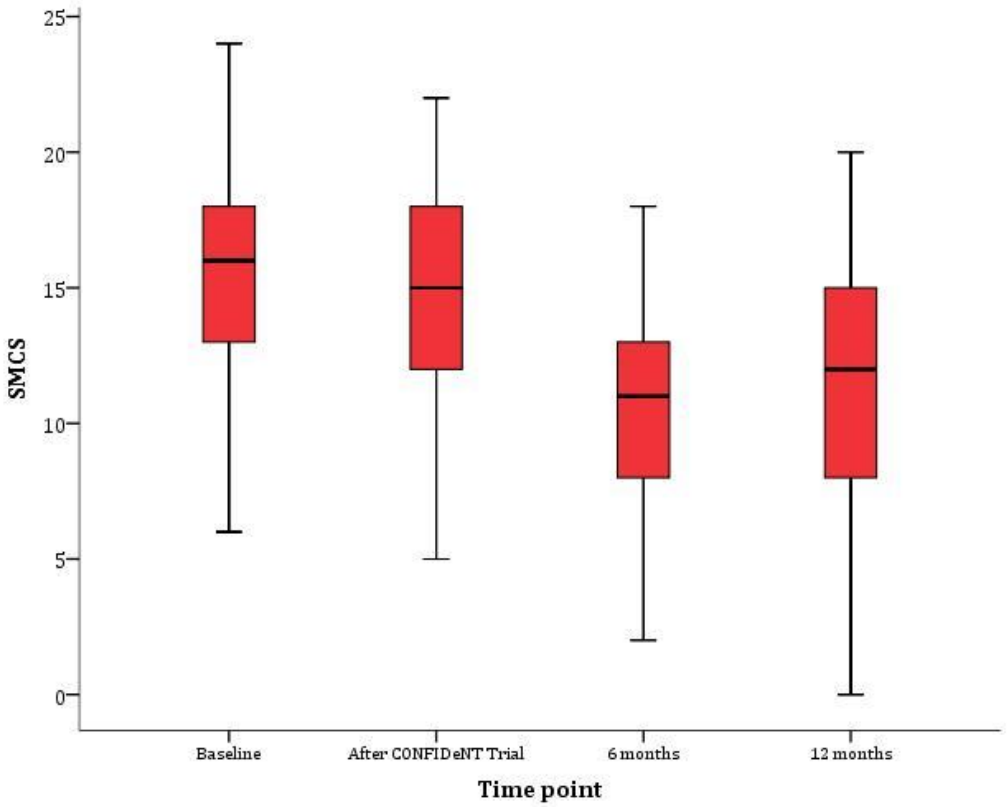
Figure 34: CONFIDeNT Follow-up Study: Weekly passive FIE: Group 3



**Baseline: n=109; After CONFIDeNT Trial: n=108; 6 months: n=72; 15 months: n=69*

The SMCS at baseline, after the CONFIDeNT Study and at 6 months and 12 months follow-up can be seen in Table 38 and Figure 35. Whilst there was no significant reduction in SMCS after the CONFIDeNT Study, patients reported a mean reduction of 5-points in the SMCS at 6 months, which was sustained at 12 months follow-up.

Figure 35: CONFIDeNT Follow-up Study: SMCS: Group 3



**Baseline: n=105; After CONFIDeNT Trial: n=102; 6 months: n=109; 12 months: n=102*

6.4 Discussion

6.4.1 Summary of results

6.4.1.1 Group 1

After the CONFIDeNT Study the proportion of patients experiencing 'treatment success' with PTNS generally improved over time from 42% after the CONFIDeNT trial to 55% at 12 months follow-up. Similarly the proportions of patients achieving a ≥25%, ≥75% and 100% reduction in weekly FIE tended to improve over the follow-up period, with the greatest improvements in the proportion of patients achieving a 100% reduction in weekly FIE. The initial significant reduction in weekly total FIE was sustained at 6 months and 12 months follow up, and this comprised a seemingly sustained reduction in weekly urge and passive FIE throughout the follow-up period. No significant improvement in SMCS was seen after the CONFIDeNT Study; however there was a 4-point reduction in SMCS at 6 and 12 months compared to baseline.

Whilst these results represent patients who had PTNS in the CONFIDeNT Trial, interpretation must be made in light of the small sample size (n=59) and the limitations of this study, which are discussed in detail in 6.4.2.

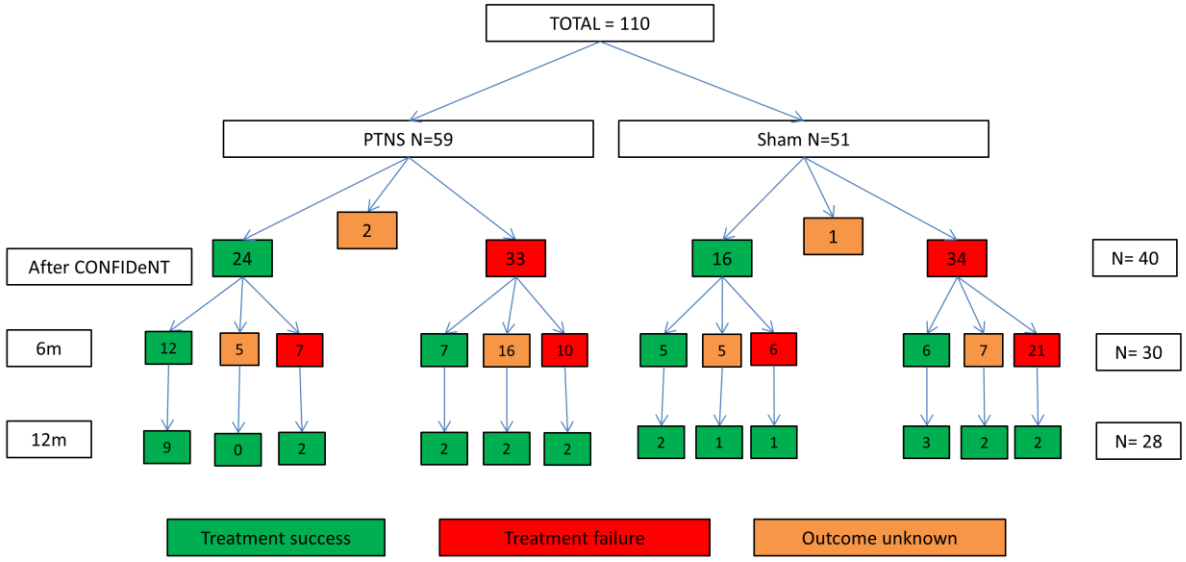
6.4.1.2 Groups 2 and 3

Interpretation of the results of the CONFIDeNT follow-up study in Groups 2 and 3 must consider the significant limitations of this study, not least as a result of the heterogeneous patient populations included. Notwithstanding these limitations, the proportions of patients experiencing 'treatment success' in each group were generally sustained over time. This was also true of the proportions of patients achieving a ≥25%, ≥75% and 100% reduction in weekly FIE. The reduction in mean total weekly FIE in both groups was generally sustained over time, with sustained reductions in

both weekly urge and passive FIE. Comparably to Group 1, whilst there was no significant reduction in SMCS after the CONFIDeNT trial, there was a 4-5 point reduction in this score at both 6 and 12 months compared to baseline in both groups.

Whilst treatment 'success rates' have been quoted, no consideration has been given to which patients this represents. To analyse this further, Figure 36 shows the number of patients with treatment success at each time point. The rate of treatment success obtained from the follow-up study group after the CONFIDeNT Study reflected the study results from the whole CONFIDeNT cohort of 227 patients (i.e. CONFIDeNT Trial 38% success in PTNS arm and 31% success in sham arm vs. follow-up study 41% in PTNS arm and 31% in sham arm). At 6 months follow-up some patients have experienced treatment success regardless of whether they had successful treatment previously, however, it is interesting to note that the highest rate of continued treatment success at 6 months and at 12 months is in the group who had successful PTNS during the CONFIDeNT Trial (at 6 months 12/24 = 50% and at 12 months 9/12 = 75%).

Figure 36: Number of patients with 'treatment success' at each follow-up time point



6.4.2 Limitations

Limitations of the study are acknowledged, and interpretation of the results must be undertaken in light of these limitations. Whilst the number of patients enrolled in the CONFIDeNT Follow-up study was considerable, since not all patients who were involved in the CONFIDeNT study were enrolled, there is inevitable attrition bias. This attrition is further evident between the 6 and 12 month follow-up time points and especially for bowel diaries which were returned only by a subset of the follow-up cohort. This potential reluctance for patients to be enrolled or remain enrolled on the CONFIDeNT Follow-up study may be a reflection of a negative result. However, the baseline demographics and characteristics of the population in the CONFIDeNT Follow-up study did mirror that in the main CONFIDeNT trial (Table 32) and in addition, the proportion of patients achieving treatment success in each arm was similar in both the CONFIDeNT Trial and the follow-up study (Figure 36). Based on this, there is no strong reason to suspect the patient sample from the CONFIDeNT follow-up study does not reflect the CONFIDeNT Trial accurately.

Further, the CONFIDeNT Follow-up study represents an observational design - in effect a case series. All sources of bias accompanied by this trial design, as discussed in Chapter 3 above, were thus re-introduced. PTNS treatment given after sham and further 'top-up' PTNS treatments were performed on an 'open-label' basis (un-blinded), and were not subject to the same strict trial conditions set out in the CONFIDeNT Trial protocol. Whilst there are not likely to be any significant differences between the treatments given within and out with the trial, this cannot be confirmed. In addition to this, the number and timing of top-up treatments delivered during the CONFIDeNT Follow-up study was not standardised or prescribed, and each centre delivered 'top-up' treatments according to local protocol. Further, some patients were given alternative treatments where PTNS had failed. Whilst these treatments were not

controlled or standardised, they were recorded in order that their effect on further outcomes could be estimated.

Finally, the limitations associated with the outcome measures chosen are also present in this study, however, for all of the same reasons as discussed in Chapter 3 above, these outcome measures were selected.

6.4.3 Interpretation of results

Overall, within the outcomes measured and considering the limitations of the study, the results of PTNS seem sustained with longer follow-up, and perhaps could be considered slightly more favourable. The primary outcome improved with time, whilst the reduction in weekly FIE was sustained. In addition to this, whilst there was no reduction in SMCS after the CONFIDeNT Study, there was a sustained reduction in SMCS of between 4 and 5 points over the follow-up period.

What is unclear is whether these findings are a result of bias, or whether there is a genuine delayed response to PTNS, i.e. there is something about the mechanism of action that means it takes longer than 14 weeks for the treatment to take effect.

An explanation for the SMCS showing no improvement immediately after PTNS treatment in the CONFIDeNT Trial despite there being a significant reduction in weekly FIE, but then showing an improvement at 6 months which is sustained at 12 months, is that this may be secondary to patient behaviour. Perhaps patients do not stop using Loperamide or incontinence pads until they are convinced of the effects of treatment. In order to test this hypothesis further analysis into which domains showed significant improvement in the SMCS was performed. When comparing the mean score for each of the domains at baseline and 6 months, there was significant reduction in the score for the frequency of FI to solid stool (mean score 2.44 +/- 1.1 to mean score 1.72 +/- 1.3, $p<0.01$), the score for the frequency of FI to liquid stool (mean score 2.50 +/- 1.2 to

mean score 1.56 =/- 1.6, p<0.01), the score for how often bowel symptoms affect lifestyle (mean score 2.45 =/- 1.4 to mean score 2.05 =/- 1.5, p<0.01 and the need to rush directly to the toilet as soon as the urge arises (mean score 3.53 +/-1.3 to mean score 1.03 =/- 1.8, p<0.01). There was however no significant reduction in incontinence pad or Loperamide usage.

Another legitimate consideration is whether results reflected patients undergoing other treatments for FI during the CONFIDeNT follow-up study time period. Patients did undergo other treatments on an open label basis, and there is no way of accounting for the contribution that other treatments have made. However, in the 24 patients who had successful PTNS in the CONFIDeNT Study, during the 12 month follow-up period, the only other FI treatments used were flax seed in one patient, occasional rectal irrigation in one patient and an increase in Loperamide in one patient. It is unlikely these treatments would have affected the outcome. Another consideration is that many centres do not use this primary outcome when considering how and when to deliver 'top-up' treatments or further therapies. The usual cut off used is patients' perception of success. If the patient perceives success, no further treatment is warranted, regardless of the 50% cut off, equally, if a patient perceives a treatment not to be successful, no further treatments may be offered despite them achieving a 50% reduction in weekly FIE.

To re-design this study and make it methodologically sound would ideally have required the continued blinding of all CONFIDeNT Trial patients and withholding of all further treatments for FI, for a period of 12 months. Unfortunately, this study design would not have been ethical, and the likelihood of patients remaining compliant would be small. An improved but ethically acceptable design could, however, have prevented attrition bias. It would have been possible to have a trial design with initial double-blinding followed by a prescribed open label period to one year follow-up. Regrettably,

while this design was considered and originally submitted for funding, it was rejected by the HTA on the basis of cost.

6.4.4 Clinical interpretation of results

The CONFIDeNT follow-up study indicates that there are a proportion of patients who do seem to respond well to PTNS, and this response is sustained for 1 year.

Further research into this treatment is essential so that we do not 'throw the baby out with the bathwater' in terms of discrediting PTNS as a valid treatment for FI. Results could be used to design further studies into the efficacy of PTNS in FI.

7 Discussion

7.1 Summary of results

Systematic review of the literature demonstrated the evidence surrounding the use of PTNS in the treatment of FI to be encouraging, however of poor quality.

The CONFIDeNT Study was therefore performed to contribute to the evidence base in this area. This was a multicentre, double-blind parallel group randomised controlled trial of PTNS vs. sham electrical stimulation in the treatment of adults with faecal incontinence. The primary outcome (proportion of patients who achieved ≥50% reduction in weekly FIE) showed no superiority of PTNS over sham electrical stimulation for the treatment of adults with FI. Whilst many of the secondary outcomes also produced a negative result, in terms of St Marks Continence Score and all quality of life measures, there was benefit of PTNS over sham stimulation in reducing mean total weekly FIE and mean weekly urge FIE.

Following the CONFIDeNT Trial, logistic regression analysis was performed to identify baseline patient characteristics, which may predict treatment outcome. The only factor identified as predicting successful PTNS in the treatment of FI, was the absence of rectal evacuatory problems at baseline. Subsequent re-analysis of the CONFIDeNT Trial results, excluding patients with any difficulties with rectal evacuation, changed the trial interpretation; more than twice as many patients in the PTNS arm than the sham arm achieved treatment success.

All patients in the CONFIDeNT Study were invited to participate in a 1-year follow-up study, the CONFIDeNT Follow-up Study. Whilst the results of this study have to be interpreted in light of significant limitations, there is evidence to suggest ongoing efficacy of PTNS in some patients, at 1 year.

7.2 Discussion of objectives

7.2.1 Objective 1: To perform a systematic review of the current evidence base for tibial nerve stimulation to treat faecal incontinence

In Chapter 3, the current literature has been searched methodically to investigate the therapeutic effect of TNS on FI in adults. Whilst a large, randomised sham controlled trial of TTNS in the treatment of FI demonstrates no significant benefit of the active treatment, a trial of similar quality in PTNS is lacking. The literature for the use of PTNS in the treatment of FI was limited and of poor quality, however, using the outcome measure chosen (treatment success indicated by at least a 50% reduction in weekly faecal incontinence episodes), the rates of treatment success were documented to be 52-82%. No definitive randomised controlled trial of PTNS had, however, been conducted to address its clinical efficacy.

7.2.2 Objective 2: To assess the short-term clinical efficacy of PTNS compared to sham electrical stimulation in the treatment of patients with significant faecal incontinence in the CONFIDeNT Study, a large multicentre randomised sham controlled trial.

The CONFIDeNT study was a definitive randomised trial, carried out to a high standard with an absence of any significant methodological flaws or serious breaches. PTNS did not show significant clinical benefit over sham electrical stimulation in the treatment of faecal incontinence based on the proportions of patients who reported at least a 50% reduction in weekly FIE (38% in PTNS arm vs. 31% in sham arm). There was however a significant improvement in those patients who had PTNS in mean reduction in total weekly FIE, urge weekly FIE and patient centred outcomes (a derivative of the ICIQ-B), compared to those who had sham.

The study was at odds with previously reported literature and reported a considerably lower rate of treatment success (38% vs. the 52-82% previously reported). It confirms the importance of well-designed randomised controlled trials to define the clinical benefit of FI treatments.

Based on this evidence presented it would be hard to justify recommending this therapy for the patient population in the trial. However, in view of the relatively low costs associated with this treatment and its high acceptability, there may be a justification for exploring the continued treatment of a subgroup of patients with troublesome urge faecal incontinence symptoms, in whom directed therapy may cause symptomatic improvement. Further studies of PTNS are warranted and should potentially be directed at those with urge FI to determine whether this approach has value.

7.2.3 Objective 3: To identify factors predictive of successful PTNS from the CONFIDeNT Study data

Logistic regression analysis identified the absence of any symptoms of rectal evacuatory difficulty as a predictor of a positive outcome with PTNS in the treatment of adults with FI. Conversely, the presence of symptoms of rectal evacuatory difficulty predicted a successful outcome with sham electrical stimulation. The presence of urge FI, isolated urge FI or urgency was, however, not predictive of treatment outcome. Interestingly, when the CONFIDeNT trial results were re-analysed, excluding patients with rectal evacuatory problems, the success rate in the PTNS arm was more than twice the rate of success in the sham arm (48.9% vs. 18.2%).

Whilst the trial was not designed to test this hypothesis, the importance of these findings is not to be underestimated. They point to a high level of placebo response amongst patients with rectal evacuatory problems, which may be very useful when

designing future trials for this problem. Equally, they indicate that perhaps patients with significant rectal evacuatory problems should be excluded from further trials of neuromodulation in the treatment of FI, and indeed there may be an argument for excluding such patients from all trials of FI. Further, there is a wider question about the symptomatology of FI, and whether the traditional subdivision of symptoms into urge and passive FI is less helpful than the subdivision into patients who have pure FI, or those who have concomitant difficulty with rectal evacuation. This will prove important for future management algorithms of FI, where difficulties of rectal evacuation might be excluded prior to embarking on some invasive or costly treatments for FI. It also raises broader questions regarding the pathophysiology of FI, and the importance of overlapping symptomatology between FI and rectal evacuatory problems.

7.2.4 Objective 4: To follow-up all patients enrolled in The CONFIDeNT Study, to assess medium-term outcomes

The CONFIDeNT Follow-up study enrolled 48% of patients from the CONFIDeNT Study, and although subject to the significant limitations discussed in detail in Chapter 6, did produce some interesting and important results. There is evidence of ongoing efficacy for a small number of patients who originally had PTNS in the CONFIDeNT Trial at 1 year follow up. Reductions in mean total weekly FIE, mean passive weekly FIE and mean urge weekly FIE tended to be sustained at 12 months. Interestingly however, the mean SMCS was apparently better at 6 and 12 months, despite this being unchanged immediately after the CONFIDeNT Trial. Further sub-analysis of the SMCS at 6 months revealed the improvement is in the areas of solid and liquid FIE, lifestyle and faecal urgency.

7.2.5 Conclusions and further researchMy experiences with this research

The CONFIDeNT Trial has, to my mind, been an extremely successful trial of an intervention, and has signified a breakthrough in research collaboration between specialist pelvic floor units in the UK. In order to ensure successful and meaningful research into pelvic floor disorders in this country, structure and collaboration are paramount. I feel research should be inclusive not exclusive, and hope the relationships forged during this trial are long-lasting and productive.

There were a few key areas which I feel contributed to the success of the trial. These included: the quality of the data (including bowel diaries) which was secondary to training of participants and trial centres with regards to compliance; effective sham stimulation; rigorous quality assurance, provided by the pragmatic clinical trials unit; patient-centred and qualitative outcome measures; and the standardised practitioner-patient interaction.

Conversely, there were elements of the trial design that I would have changed, if given the opportunity over again. Firstly, I would have considered patient weight/BMI, menopausal status and employment status at the outset. Whilst I do not feel these data would have changed results significantly, they may have provided interesting post hoc analyses. I would re-write the bowel diary, to include consistency of every bowel movement, include use of constipating medication, and generally make it slightly more user-friendly. As mentioned previously, the development of an app to capture these data would be fantastic, but costly!

In addition to these changes, I would have asked all participants specific 'tick box' style questions about previous treatments and past medical history in order to attempt subgrouping of patients in an effort to reduce heterogeneity of the population. Whilst this may not have been helpful, it may have helped in defining where in the algorithm

of treatment PTNS has most efficacy. I would also have liked to reduce the questionnaire burden and used more up-to-date questionnaires, such as PAC-QOL and PAC-SYM, including those which concentrate more on the link between FI and RED. Finally, I also wish there had been the originally planned, robust follow up study, blinding patients for a longer period of follow-up. The obvious ethical, financial and logistical problems result in huge obstacles to this however.

7.2.6 Future work

I consider the term 'future work' has two key elements, and I should like to explore these separately. The first is where I consider the general key focuses in FI research should be; and the second is where I think the priorities lie regarding research into PTNS, in light of the CONFIDeNT Trial results. I describe the issues this way round, as I feel it would be helpful to address the more general issues prior to embarking on further specific work.

International collaboration by all stakeholders in FI and/or anal incontinence should be established, and seek to set a few standards that all literature and research should conform to, to enable comparisons to be made. These include:

A standardised global definition of faecal and anal incontinence

Agreement on FI sub-types, specifically whether the current classification of urge and passive incontinence are useful, or whether new definitions based on pure FI or overlapping RED should be used. These definitions should be accompanied by anorectal physiological guidelines and definitions.

Minimum FI symptom requirement for patient to be eligible for trial inclusion

Choice of the 'best' primary and secondary endpoints for studies of FI

Algorithm detailing rationale and order of treatments given for FI

Once agreement has been reached, future research into PTNS in the treatment of FI would be much more straightforward. To my mind, future research priorities in terms of PTNS in light of the CONFIDeNT Trial results include answers to the following questions:

Does PTNS have good efficacy compared to sham for patients with pure FI?

At what follow-up time period should PTNS be assessed in studies?

What is the optimal PTNS treatment duration?

In order to answer these questions, I would suggest designing a further parallel group, sham-controlled, double blind RCT, similar to that of the CONFIDeNT Study. Recruitment to this study would be in line with the agreed standard definition of FI, with patients fulfilling the agreed minimum FI symptom requirement. Patients would have pure FI, as based on the agreed anorectal physiological definitions. Treatment would be given at the time point agreed in the algorithm, and outcome measures would be those agreed by the international collaboration. Trial design would be similar to the CONFIDeNT Trial in other respects, including measuring outcomes after 6 and 12 weeks treatment. In addition to this, a longer period of blinded follow up, up to 1 year, would be added, and then a structured and monitored extended follow-up where patients were permitted certain other treatments also under trial conditions. Whilst such a trial would be extremely robust, it would unfortunately involve a large workload with significant cost.

7.2.7 Key clinical messages

The CONFIDeNT Trial has shown PTNS to have no superiority over sham electrical stimulation in the treatment of unselected adults with FI, based on the primary outcome measure chosen. There is however some evidence to suggest treatment

efficacy in those with urge FI, and in addition, potentially higher success rates in patients who experience no concomitant problems with rectal evacuation.

Based on my experience of this thesis, I would advocate that PTNS should not be used as a 'blanket first line treatment' for all patients with FI. I feel it also very important to highlight however that there are clearly some patients who do receive significant benefit from treatment. I feel that my research should mark the beginning of a large body of work into which subgroups of patients benefit from PTNS, and where it best fits into a carefully designed algorithm of care. Allied research into a likely mechanism of action may also help this process significantly.

8 References

1. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. Journal of gastrointestinal and liver diseases : JGLD. 2006;15(3):237-41. Epub 2006/10/03.
2. Nelson R, Norton N, Cautley E, Furner S. Community-based prevalence of anal incontinence. JAMA : the journal of the American Medical Association. 1995;274(7):559-61. Epub 1995/08/16.
3. Rao SS, American College of Gastroenterology Practice Parameters C. Diagnosis and management of fecal incontinence. American College of Gastroenterology Practice Parameters Committee. The American journal of gastroenterology. 2004;99(8):1585-604. Epub 2004/08/17.
4. Madoff RD, Parker SC, Varma MG, Lowry AC. Faecal incontinence in adults. Lancet. 2004;364(9434):621-32. Epub 2004/08/18.
5. Rao SS. Pathophysiology of adult fecal incontinence. Gastroenterology. 2004;126(1 Suppl 1):S14-22. Epub 2004/02/24.
6. Lunniss PJ, Gladman MA, Hetzer FH, Williams NS, Scott SM. Risk factors in acquired faecal incontinence. Journal of the Royal Society of Medicine. 2004;97(3):111-6. Epub 2004/03/05.
7. Barleben A, Mills S. Anorectal anatomy and physiology. The Surgical clinics of North America. 2010;90(1):1-15, Table of Contents. Epub 2010/01/30.
8. Bajwa A, Emmanuel A. The physiology of continence and evacuation. Best practice & research Clinical gastroenterology. 2009;23(4):477-85. Epub 2009/08/04.
9. Matzel KE, Schmidt RA, Tanagho EA. Neuroanatomy of the striated muscular anal continence mechanism. Implications for the use of neurostimulation. Diseases of the colon and rectum. 1990;33(8):666-73. Epub 1990/08/01.
10. Munsat TL. Neurologic Bladder, Bowel and Sexual Dysfunction. Elsevier Science Limited, 2001. p. 27-37.
11. Kunze WA, Furness JB. The enteric nervous system and regulation of intestinal motility. Annual review of physiology. 1999;61:117-42. Epub 1999/04/01.
12. Frenckner B, Euler CV. Influence of pudendal block on the function of the anal sphincters. Gut. 1975;16(6):482-9. Epub 1975/06/01.
13. Scott SM, Lunniss PJ. Risk Factors in Faecal Incontinence. Chapter 5. Faecal Incontinence, Diagnosis and Treatment. 2007. Springer Milan DOI 10.1007/978-88-470-0638-6
14. Salmons S, Vrbova G. The influence of activity on some contractile characteristics of mammalian fast and slow muscles. The Journal of physiology. 1969;201(3):535-49. Epub 1969/05/01.
15. Johnson MA, Polgar J, Weightman D, Appleton D. Data on the distribution of fibre types in thirty-six human muscles. An autopsy study. Journal of the neurological sciences. 1973;18(1):111-29. Epub 1973/01/01.
16. Kerremans R. Electrical activity and motility of the internal anal sphincter: an "in vivo" electrophysiological study in man. Acta gastro-enterologica Belgica. 1968;31(7):465-82. Epub 1968/07/01.
17. Wankling WJ, Brown BH, Collins CD, Duthie HL. Basal electrical activity in the anal canal in man. Gut. 1968;9(4):457-60. Epub 1968/08/01.
18. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure. An in vivo and in vitro study in man. International journal of colorectal disease. 1989;4(2):118-22. Epub 1989/01/01.
19. Gibbons CP, Trowbridge EA, Bannister JJ, Read NW. Role of anal cushions in maintaining continence. Lancet. 1986;1(8486):886-8. Epub 1986/04/19.

20. Parks AG, Porter NH, Hardcastle J. The syndrome of the descending perineum. Proceedings of the Royal Society of Medicine. 1966;59(6):477-82. Epub 1966/06/01.
21. Palit S, Lunniss PJ, Scott SM. The physiology of human defecation. Digestive diseases and sciences. 2012;57(6):1445-64. Epub 2012/03/01.
22. Rao SS, Sadeghi P, Beaty J, Kavlock R, Ackerson K. Ambulatory 24-h colonic manometry in healthy humans. American journal of physiology Gastrointestinal and liver physiology. 2001;280(4):G629-39. Epub 2001/03/20.
23. Dinning PG, Zarate N, Szczesniak MM, Mohammed SD, Preston SL, Fairclough PD, et al. Bowel preparation affects the amplitude and spatiotemporal organization of colonic propagating sequences. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2010;22(6):633-e176. Epub 2010/02/26.
24. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. Prolonged multi-point recording of colonic manometry in the unprepared human colon: providing insight into potentially relevant pressure wave parameters. The American journal of gastroenterology. 2001;96(6):1838-48. Epub 2001/06/23.
25. Miller R, Lewis GT, Bartolo DC, Cervero F, Mortensen NJ. Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique. The British journal of surgery. 1988;75(10):1003-7. Epub 1988/10/01.
26. Miller R, Bartolo DC, Cervero F, Mortensen NJ. Anorectal sampling: a comparison of normal and incontinent patients. The British journal of surgery. 1988;75(1):44-7. Epub 1988/01/01.
27. Carrington EVH, A.; Knowles, C. H.; Lunniss, P. J.; Scott, S. M. Characterizations of Transient Anal Sphincter Relaxations (TASRs) in health using high resolution anorectal manometry: Redifining the sampling reflex? Digestive Diseases Week; May 2013; Orlando, USA: Gastroenterology; 2013. p. S-745.
28. Martelli H, Devroede G, Arhan P, Duguay C, Dornic C, Faverdin C. Some parameters of large bowel motility in normal man. Gastroenterology. 1978;75(4):612-8. Epub 1978/10/01.
29. Meunier P, Mollard P, Marechal JM. Physiopathology of megarectum: the association of megarectum with encopresis. Gut. 1976;17(3):224-7. Epub 1976/03/01.
30. Sun WM, Read NW, Miner PB. Relation between rectal sensation and anal function in normal subjects and patients with faecal incontinence. Gut. 1990;31(9):1056-61. Epub 1990/09/01.
31. Broens PM, Penninckx FM, Lestar B, Kerremans RP. The trigger for rectal filling sensation. International journal of colorectal disease. 1994;9(1):1-4. Epub 1994/04/01.
32. Gladman MA, Lunniss PJ, Scott SM, Swash M. Rectal hyposensitivity. The American journal of gastroenterology. 2006;101(5):1140-51. Epub 2006/05/16.
33. Scharli AF, Kiesewetter WB. Defecation and continence: some new concepts. Diseases of the colon and rectum. 1970;13(2):81-107. Epub 1970/03/01.
34. Lubowski DZ, Meagher AP, Smart RC, Butler SP. Scintigraphic assessment of colonic function during defaecation. International journal of colorectal disease. 1995;10(2):91-3. Epub 1995/01/01.
35. Lynch AC, Anthony A, Dobbs BR, Frizelle FA. Anorectal physiology following spinal cord injury. Spinal cord. 2000;38(10):573-80. Epub 2000/11/28.
36. McCrea GL, Miaskowski C, Stotts NA, Macera L, Varma MG. Pathophysiology of constipation in the older adult. World journal of gastroenterology : WJG. 2008;14(17):2631-8. Epub 2008/05/08.
37. Nakanishi N, Tatara K, Shinsho F, Murakami S, Takatorige T, Fukuda H, et al. Mortality in relation to urinary and faecal incontinence in elderly people living at home. Age and ageing. 1999;28(3):301-6. Epub 1999/09/04.

38. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Digestive diseases and sciences. 1993;38(9):1569-80. Epub 1993/09/01.
39. Edwards NI, Jones D. The prevalence of faecal incontinence in older people living at home. Age and ageing. 2001;30(6):503-7. Epub 2001/12/18.
40. Johanson JF, Lafferty J. Epidemiology of fecal incontinence: the silent affliction. The American journal of gastroenterology. 1996;91(1):33-6. Epub 1996/01/01.
41. Leigh RJ, Turnberg LA. Faecal incontinence: the unvoiced symptom. Lancet. 1982;1(8285):1349-51. Epub 1982/06/12.
42. Rizk DE, Hassan MY, Shaheen H, Cherian JV, Micallef R, Dunn E. The prevalence and determinants of health care-seeking behavior for fecal incontinence in multiparous United Arab Emirates females. Diseases of the colon and rectum. 2001;44(12):1850-6. Epub 2001/12/14.
43. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. BJOG : an international journal of obstetrics and gynaecology. 2000;107(12):1460-70. Epub 2001/02/24.
44. Lam, Kennedy, Chen, Lubowski, Talley. Prevalence of faecal incontinence: obstetric and constipation-related risk factors; a population-based study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 1999;1(4):197-203. Epub 1999/07/01.
45. Kalantar JS, Howell S, Talley NJ. Prevalence of faecal incontinence and associated risk factors; an underdiagnosed problem in the Australian community? The Medical journal of Australia. 2002;176(2):54-7. Epub 2002/04/09.
46. Lynch AC, Dobbs BR, Keating J, Frizelle FA. The prevalence of faecal incontinence and constipation in a general New Zealand population; a postal survey. The New Zealand medical journal. 2001;114(1142):474-7. Epub 2002/01/05.
47. Giebel GD, Lefering R, Troidl H, Blochl H. Prevalence of fecal incontinence: what can be expected? International journal of colorectal disease. 1998;13(2):73-7. Epub 1998/06/25.
48. Santos VL, Domansky Rde C, Hanate C, Matos DS, Benvenuto CV, Jorge JM. Self-reported fecal incontinence in a community-dwelling, urban population in southern Brazil. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN. 2014;41(1):77-83. Epub 2014/01/01.
49. Thomas TM, Egan M, Walgrove A, Meade TW. The prevalence of faecal and double incontinence. Community medicine. 1984;6(3):216-20. Epub 1984/08/01.
50. Whitehead WE, Borrud L, Goode PS, Meikle S, Mueller ER, Tuteja A, et al. Fecal incontinence in US adults: epidemiology and risk factors. Gastroenterology. 2009;137(2):512-7, 7 e1-2. Epub 2009/05/05.
51. Siproudhis L, Pigot F, Godeberge P, Damon H, Soudan D, Bigard MA. Defecation disorders: a French population survey. Diseases of the colon and rectum. 2006;49(2):219-27. Epub 2005/12/20.
52. Kamm MA, Farthing MJ, Lennard-Jones JE, Perry LA, Chard T. Steroid hormone abnormalities in women with severe idiopathic constipation. Gut. 1991;32(1):80-4. Epub 1991/01/01.
53. Perry S, Shaw C, McGrother C, Matthews RJ, Assassa RP, Dallosso H, et al. Prevalence of faecal incontinence in adults aged 40 years or more living in the community. Gut. 2002;50(4):480-4. Epub 2002/03/13.
54. Verhagen TE, Lagro-Janssen AL. [Fecal incontinence in community-dwelling elderly: findings from a study of prevalence, consultation of physicians, psychosocial aspects and treatment]. Nederlands tijdschrift voor geneeskunde. 2001;145(15):741-4.

Epub 2001/05/03. Fecale incontinentie bij zelfstandig wonende ouderen: onderzoeksresultaten naar voorkomen, hulpvraaggedrag, psychosociale aspecten en behandeling.
55. Talley NJ, O'Keefe EA, Zinsmeister AR, Melton LJ, 3rd. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. Gastroenterology. 1992;102(3):895-901. Epub 1992/03/01.
56. O'Keefe EA, Talley NJ, Zinsmeister AR, Jacobsen SJ. 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. 1995;50(4):M184-9. Epub 1995/07/01.
57. Nakanishi N, Tatara K, Nakajima K, Takabayashi H, Takahashi S, Naramura H, et al. [Urinary and fecal incontinence in a community-residing elderly population: prevalence, correlates and prognosis]. [Nihon koshu eisei zasshi] Japanese journal of public health. 1997;44(3):192-200. Epub 1997/03/01.
58. Campbell AJ, Reinken J, McCosh L. Incontinence in the elderly: prevalence and prognosis. Age and ageing. 1985;14(2):65-70. Epub 1985/03/01.
59. Roberts RO, Jacobsen SJ, Reilly WT, Pemberton JH, Lieber MM, Talley NJ. Prevalence of combined fecal and urinary incontinence: a community-based study. Journal of the American Geriatrics Society. 1999;47(7):837-41. Epub 1999/07/15.
60. Hellstrom L, Ekelund P, Milsom I, Skoog I. The influence of dementia on the prevalence of urinary and faecal incontinence in 85-year-old men and women. Archives of gerontology and geriatrics. 1994;19(1):11-20. Epub 1994/07/01.
61. Kok AL, Voorhorst FJ, Burger CW, van Houten P, Kenemans P, Janssens J. Urinary and faecal incontinence in community-residing elderly women. Age and ageing. 1992;21(3):211-5. Epub 1992/05/01.
62. Borrie MJ, Davidson HA. Incontinence in institutions: costs and contributing factors. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 1992;147(3):322-8. Epub 1992/08/01.
63. Chassagne P, Landrin I, Neveu C, Czernichow P, Bouaniche M, Doucet J, et al. Fecal incontinence in the institutionalized elderly: incidence, risk factors, and prognosis. The American journal of medicine. 1999;106(2):185-90. Epub 1999/05/07.
64. Topinkova E, Neuwirth J, Stankova M, Mellanova A, Haas T. [Urinary and fecal incontinence in geriatric facilities in the Czech Republic]. Casopis lekaru ceskych. 1997;136(18):573-7. Epub 1998/05/26. Inkontinence moci a stolice v geriatrickych zarizenich v Ceske Republice.
65. Nelson R, Furner S, Jesudason V. Fecal incontinence in Wisconsin nursing homes: prevalence and associations. Diseases of the colon and rectum. 1998;41(10):1226-9. Epub 1998/10/27.
66. Nelson RL. Epidemiology of fecal incontinence. Gastroenterology. 2004;126(1 Suppl 1):S3-7. Epub 2004/02/24.
67. Chapman AE, Geerdes B, Hewett P, Young J, Eyers T, Kiroff G, et al. Systematic review of dynamic graciloplasty in the treatment of faecal incontinence. The British journal of surgery. 2002;89(2):138-53. Epub 2002/02/22.
68. Tilvis RS, Hakala SM, Valvanne J, Erkinjuntti T. Urinary incontinence as a predictor of death and institutionalization in a general aged population. Archives of gerontology and geriatrics. 1995;21(3):307-15. Epub 1995/11/01.
69. Tsuji I, Whalen S, Finucane TE. Predictors of nursing home placement in community-based long-term care. Journal of the American Geriatrics Society. 1995;43(7):761-6. Epub 1995/07/01.
70. Sanford JR. Tolerance of debility in elderly dependants by supporters at home: its significance for hospital practice. Br Med J. 1975;3(5981):471-3. Epub 1975/08/23.
71. Porell F, Caro FG, Silva A, Monane M. A longitudinal analysis of nursing home outcomes. Health services research. 1998;33(4 Pt 1):835-65. Epub 1998/10/20.

72. Varma MG, Brown JS, Creasman JM, Thom DH, Van Den Eeden SK, Beattie MS, et al. Fecal incontinence in females older than aged 40 years: who is at risk? Diseases of the colon and rectum. 2006;49(6):841-51. Epub 2006/06/03.
73. Berger MB, Delancey JO, Fenner DE. Racial differences in fecal incontinence in community-dwelling women from the EPI study. Female pelvic medicine & reconstructive surgery. 2013;19(3):169-74. Epub 2013/04/25.
74. Howard D, Davies PS, DeLancey JO, Small Y. Differences in perineal lacerations in black and white primiparas. Obstetrics and gynecology. 2000;96(4):622-4. Epub 2000/09/27.
75. Angioli R, Gomez-Marin O, Cantuaria G, O'Sullivan M J. Severe perineal lacerations during vaginal delivery: the University of Miami experience. American journal of obstetrics and gynecology. 2000;182(5):1083-5. Epub 2000/05/20.
76. Handa VL, Danielsen BH, Gilbert WM. Obstetric anal sphincter lacerations. Obstetrics and gynecology. 2001;98(2):225-30. Epub 2001/08/17.
77. Bharucha AE, Fletcher JG, Harper CM, Hough D, Daube JR, Stevens C, et al. Relationship between symptoms and disordered continence mechanisms in women with idiopathic fecal incontinence. Gut. 2005;54:546-55.
78. Sun WM, Donnelly TC, Read NW. Utility of a combined test of anorectal manometry, electromyography, and sensation in determining the mechanism of 'idiopathic' faecal incontinence. Gut. 1992;33(6):807-13. Epub 1992/06/01.
79. Bartolo DC, Jarratt JA, Read MG, Donnelly TC, Read NW. The role of partial denervation of the puborectalis in idiopathic faecal incontinence. The British journal of surgery. 1983;70(11):664-7.
80. Chun AB, Rose S, Mitrani C, Silvestre AJ, Wald A. Anal sphincter structure and function in homosexual males engaging in anoreceptive intercourse. The American journal of gastroenterology. 1997;92(3):465-8.
81. Mitrani C, Chun A, Desautels S, Wald A. Anorectal manometric characteristics in men and women with idiopathic fecal incontinence. Journal of clinical gastroenterology. 1998;26(3):175-8.
82. Chen H, Humphreys MS, Kettlewell MG, Bulkley GB, Mortensen N, George BD. Anal ultrasound predicts the response to nonoperative treatment of fecal incontinence in men. Annals of surgery. 1999;229(5):739-43; discussion 43.
83. Paramor KA, Ibrahim QI, Sadowski DC. Clinical parameters and symptom severity in males with fecal leakage and incontinence. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2014;26(3):361-7. Epub 2013/12/18.
84. Rao SS, Ozturk R, Stessman M. Investigation of the pathophysiology of fecal seepage. American Journal of Gastroenterology. 2004;99(11):2204-9.
85. Parellada CM, Miller AS, Williamson ME, Johnston D. Paradoxical high anal resting pressures in men with idiopathic fecal seepage. Diseases of the colon and rectum. 1998;41(5):593-7.
86. Buser WD, Miner PB. Delayed rectal sensation with fecal incontinence. Successful treatment using anorectal manometry. Gastroenterology. 1986;91(5):1186-91.
87. Felt-Bersma RJ, Sloots CE, Poen AC, Cuesta MA, Meuwissen SG. Rectal compliance as a routine measurement: extreme volumes have direct clinical impact and normal volumes exclude rectum as a problem. Diseases of the Colon & Rectum. 2000;43(12):1732-8.
88. Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. Psychological impact and risk factors associated with new onset fecal incontinence. Journal of psychosomatic research. 2012;73(6):464-8.

89. Smith TM, Menees SB, Xu X, Saad RJ, Chey WD, Fenner DE. Factors associated with quality of life among women with fecal incontinence. International urogynecology journal. 2013;24(3):493-9.
90. Rao SS, Patel RS. How useful are manometric tests of anorectal function in the management of defecation disorders? The American journal of gastroenterology. 1997;92(3):469-75. Epub 1997/03/01.
91. Kamm MA. Obstetric damage and faecal incontinence. Lancet. 1994;344(8924):730-3. Epub 1994/09/10.
92. Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery. The New England journal of medicine. 1993;329(26):1905-11. Epub 1993/12/23.
93. Law PJ, Kamm MA, Bartram CI. Anal endosonography in the investigation of faecal incontinence. The British journal of surgery. 1991;78(3):312-4. Epub 1991/03/01.
94. Swash M. Faecal incontinence. Bmj. 1993;307(6905):636-7. Epub 1993/09/11.
95. Thakar R, Sultan AH. Management of obstetric anal sphincter injury. The Obstetrician & Gynaecologist. 2003;5(2):72-8.
96. McCandlish R, Bowler U, van Asten H, Berridge G, Winter C, Sames L, et al. A randomised controlled trial of care of the perineum during second stage of normal labour. British journal of obstetrics and gynaecology. 1998;105(12):1262-72. Epub 1999/01/12.
97. Schiller LR, Santa Ana CA, Schmulen AC, Hendler RS, Harford WV, Fordtran JS. Pathogenesis of fecal incontinence in diabetes mellitus: evidence for internal-anal-sphincter dysfunction. The New England journal of medicine. 1982;307(27):1666-71. Epub 1982/12/30.
98. Pollack J, Nordenstam J, Brismar S, Lopez A, Altman D, Zetterstrom J. Anal incontinence after vaginal delivery: a five-year prospective cohort study. Obstetrics and gynecology. 2004;104(6):1397-402. Epub 2004/12/02.
99. Lone F, Sultan A, Thakar R. Obstetric pelvic floor and anal sphincter injuries. The Obstetrician & Gynaecologist. 2012;14(4):257-66.
100. Quinn M. Obstetric denervation-gynaecological reinnervation: disruption of the inferior hypogastric plexus in childbirth as a source of gynaecological symptoms. Medical hypotheses. 2004;63(3):390-3. Epub 2004/08/04.
101. Kiff ES, Swash M. Slowed conduction in the pudendal nerves in idiopathic (neurogenic) faecal incontinence. The British journal of surgery. 1984;71(8):614-6. Epub 1984/08/01.
102. Donnelly V, Fynes M, Campbell D, Johnson H, O'Connell PR, O'Herlihy C. Obstetric events leading to anal sphincter damage. Obstetrics and gynecology. 1998;92(6):955-61. Epub 1998/12/05.
103. Kamm MA. Faecal incontinence. Bmj. 1998;316(7130):528-32. Epub 1998/03/21.
104. Nielsen MB, Hauge C, Pedersen JF, Christiansen J. Endosonographic evaluation of patients with anal incontinence: findings and influence on surgical management. AJR American journal of roentgenology. 1993;160(4):771-5. Epub 1993/04/01.
105. Fernando R, Sultan AH, Kettle C, Thakar R, Radley S. Methods of repair for obstetric anal sphincter injury. The Cochrane database of systematic reviews. 2006(3):CD002866. Epub 2006/07/21.
106. Abramowitz L, Sobhani I, Ganansia R, Vuagnat A, Benifla JL, Darai E, et al. Are sphincter defects the cause of anal incontinence after vaginal delivery? Results of a prospective study. Diseases of the colon and rectum. 2000;43(5):590-6; discussion 6-8. Epub 2000/05/29.

107. Chaliha C, Sultan AH, Bland JM, Monga AK, Stanton SL. Anal function: effect of pregnancy and delivery. American journal of obstetrics and gynecology. 2001;185(2):427-32. Epub 2001/08/24.
108. Fynes M, Donnelly V, Behan M, O'Connell PR, O'Herlihy C. Effect of second vaginal delivery on anorectal physiology and faecal continence: a prospective study. Lancet. 1999;354(9183):983-6. Epub 1999/09/29.
109. Belmonte-Montes C, Hagerman G, Vega-Yepez PA, Hernandez-de-Anda E, Fonseca-Morales V. Anal sphincter injury after vaginal delivery in primiparous females. Diseases of the colon and rectum. 2001;44(9):1244-8. Epub 2001/10/05.
110. Nazir M, Carlsen E, Nesheim BI. Do occult anal sphincter injuries, vector volume manometry and delivery variables have any predictive value for bowel symptoms after first time vaginal delivery without third and fourth degree rupture? A prospective study. Acta obstetricia et gynecologica Scandinavica. 2002;81(8):720-6. Epub 2002/08/14.
111. Pinta TM, Kylanpaa ML, Teramo KA, Luukkonen PS. Sphincter rupture and anal incontinence after first vaginal delivery. Acta obstetricia et gynecologica Scandinavica. 2004;83(10):917-22. Epub 2004/09/30.
112. Damon H, Bretones S, Henry L, Mellier G, Mion F. Long-term consequences of first vaginal delivery-induced anal sphincter defect. Diseases of the colon and rectum. 2005;48(9):1772-6. Epub 2005/06/28.
113. Faltin DL, Boulvain M, Irion O, Bretones S, Stan C, Weil A. Diagnosis of anal sphincter tears by postpartum endosonography to predict fecal incontinence. Obstetrics and gynecology. 2000;95(5):643-7. Epub 2000/04/25.
114. Lunniss PJ, Scott SM. Pathophysiology of Anal Incontinence Chapter 8..
115. Varma A, Gunn J, Gardiner A, Lindow SW, Duthie GS. Obstetric anal sphincter injury: prospective evaluation of incidence. Diseases of the colon and rectum. 1999;42(12):1537-43. Epub 1999/12/29.
116. Oberwalder M, Connor J, Wexner SD. Meta-analysis to determine the incidence of obstetric anal sphincter damage. The British journal of surgery. 2003;90(11):1333-7. Epub 2003/11/05.
117. Zetterstrom J, Lopez A, Holmstrom B, Nilsson BY, Tisell A, Anzen B, et al. Obstetric sphincter tears and anal incontinence: an observational follow-up study. Acta obstetricia et gynecologica Scandinavica. 2003;82(10):921-8. Epub 2003/09/06.
118. Dupuis O, Madelenat P, Rudigoz RC. [Fecal and urinary incontinence after delivery: risk factors and prevention]. Gynecologie, obstetrique & fertilite. 2004;32(6):540-8. Epub 2004/06/26. Incontinences urinaires et anales post-obstetricales: facteurs de risque et prevention.
119. Sultan AH, Kamm MA, Bartram CI, Hudson CN. Anal sphincter trauma during instrumental delivery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 1993;43(3):263-70. Epub 1993/12/01.
120. Fraser WD, Marcoux S, Krauss I, Douglas J, Goulet C, Boulvain M. Multicenter, randomized, controlled trial of delayed pushing for nulliparous women in the second stage of labor with continuous epidural analgesia. The PEOPLE (Pushing Early or Pushing Late with Epidural) Study Group. American journal of obstetrics and gynecology. 2000;182(5):1165-72. Epub 2000/05/20.
121. Cheng YW, Hopkins LM, Caughey AB. How long is too long: Does a prolonged second stage of labor in nulliparous women affect maternal and neonatal outcomes? American journal of obstetrics and gynecology. 2004;191(3):933-8. Epub 2004/10/07.
122. Sultan AH, Kamm MA, Hudson CN, Bartram CI. Third degree obstetric anal sphincter tears: risk factors and outcome of primary repair. Bmj. 1994;308(6933):887-91. Epub 1994/04/02.

123. Kabiru W, Raynor BD. Obstetric outcomes associated with increase in BMI category during pregnancy. American journal of obstetrics and gynecology. 2004;191(3):928-32. Epub 2004/10/07.
124. Castro LC, Avina RL. Maternal obesity and pregnancy outcomes. Current opinion in obstetrics & gynecology. 2002;14(6):601-6. Epub 2002/11/21.
125. Roman H, Robillard PY, Payet E, El Amrani R, Verspyck E, Marpeau L, et al. [Factors associated with fecal incontinence after childbirth. Prospective study in 525 women]. Journal de gynecologie, obstetrique et biologie de la reproduction. 2004;33(6 Pt 1):497-505. Epub 2004/11/30. Facteurs lies a l'incontinence anale du post-partum. Etude prospective chez 525 femmes.
126. Benavides L, Wu JM, Hundley AF, Ivester TS, Visco AG. The impact of occiput posterior fetal head position on the risk of anal sphincter injury in forceps-assisted vaginal deliveries. American journal of obstetrics and gynecology. 2005;192(5):1702-6. Epub 2005/05/20.
127. Engel AF, Kamm MA, Bartram CI, Nicholls RJ. Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. International journal of colorectal disease. 1995;10(3):152-5. Epub 1995/01/01.
128. Wu JM, Williams KS, Hundley AF, Connolly A, Visco AG. Occiput posterior fetal head position increases the risk of anal sphincter injury in vacuum-assisted deliveries. American journal of obstetrics and gynecology. 2005;193(2):525-8; discussion 8-9. Epub 2005/08/16.
129. Roos AM, Thakar R, Sultan AH. Outcome of primary repair of obstetric anal sphincter injuries (OASIS): does the grade of tear matter? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;36(3):368-74. Epub 2010/01/14.
130. Willis S, Faridi A, Schelzig S, Hoelzl F, Kasperk R, Rath W, et al. Childbirth and incontinence: a prospective study on anal sphincter morphology and function before and early after vaginal delivery. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie. 2002;387(2):101-7. Epub 2002/07/12.
131. Snooks SJ, Swash M, Henry MM, Setchell M. Risk factors in childbirth causing damage to the pelvic floor innervation. International journal of colorectal disease. 1986;1(1):20-4. Epub 1986/01/01.
132. Snooks SJ, Swash M, Mathers SE, Henry MM. Effect of vaginal delivery on the pelvic floor: a 5-year follow-up. The British journal of surgery. 1990;77(12):1358-60. Epub 1990/12/01.
133. Rieger N, Wattchow D. The effect of vaginal delivery on anal function. The Australian and New Zealand journal of surgery. 1999;69(3):172-7. Epub 1999/03/13.
134. Kiff ES, Barnes PR, Swash M. Evidence of pudendal neuropathy in patients with perineal descent and chronic straining at stool. Gut. 1984;25(11):1279-82. Epub 1984/11/01.
135. Engel AF, Kamm MA. The acute effect of straining on pelvic floor neurological function. International journal of colorectal disease. 1994;9(1):8-12. Epub 1994/04/01.
136. Jameson JS, Chia YW, Kamm MA, Speakman CT, Chye YH, Henry MM. Effect of age, sex and parity on anorectal function. The British journal of surgery. 1994;81(11):1689-92. Epub 1994/11/01.
137. Nelson RL, Furner SE, Westercamp M, Farquhar C. Cesarean delivery for the prevention of anal incontinence. Cochrane database of systematic reviews. 2010(2):CD006756. Epub 2010/02/19.
138. Gyhagen M, Bullarbo M, Nielsen TF, Milsom I. Faecal incontinence 20 years after one birth: a comparison between vaginal delivery and caesarean section. International urogynecology journal. 2014;25(10):1411-8. Epub 2014/05/08.

139. Boreham MK, Richter HE, Kenton KS, Nager CW, Gregory WT, Aronson MP, et al. Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life. American journal of obstetrics and gynecology. 2005;192(5):1637-42. Epub 2005/05/20.
140. Uustal Fornell E, Wingren G, Kjolhede P. Factors associated with pelvic floor dysfunction with emphasis on urinary and fecal incontinence and genital prolapse: an epidemiological study. Acta obstetricia et gynecologica Scandinavica. 2004;83(4):383-9. Epub 2004/03/10.
141. Goode PS, Burgio KL, Halli AD, Jones RW, Richter HE, Redden DT, et al. Prevalence and correlates of fecal incontinence in community-dwelling older adults. Journal of the American Geriatrics Society. 2005;53(4):629-35. Epub 2005/04/09.
142. Lysy J, Israeli E, Goldin E. The prevalence of chronic diarrhea among diabetic patients. The American journal of gastroenterology. 1999;94(8):2165-70. Epub 1999/08/13.
143. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. Archives of internal medicine. 2001;161(16):1989-96. Epub 2001/09/26.
144. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. The American journal of gastroenterology. 2005;100(5):1174-84. Epub 2005/04/22.
145. Sauter GH, Moussavian AC, Meyer G, Steitz HO, Parhofer KG, Jungst D. Bowel habits and bile acid malabsorption in the months after cholecystectomy. The American journal of gastroenterology. 2002;97(7):1732-5. Epub 2002/07/24.
146. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T, et al. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstetrics and gynecology. 2001;97(1):116-20. Epub 2001/01/12.
147. Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA : the journal of the American Medical Association. 2005;293(8):935-48. Epub 2005/02/25.
148. Kim T, Chae G, Chung SS, Sands DR, Speranza JR, Weiss EG, et al. Faecal incontinence in male patients. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2008;10(2):124-30. Epub 2007/05/15.
149. Di Lorenzo C, Benninga MA. Pathophysiology of pediatric fecal incontinence. Gastroenterology. 2004;126(1 Suppl 1):S33-40. Epub 2004/02/24.
150. Read NW, Abouzekry L, Read MG, Howell P, Ottewell D, Donnelly TC. Anorectal function in elderly patients with fecal impaction. Gastroenterology. 1985;89(5):959-66. Epub 1985/11/01.
151. Burgell RE, Bhan C, Lunniss PJ, Scott SM. Fecal incontinence in men: coexistent constipation and impact of rectal hyposensitivity. Diseases of the colon and rectum. 2012;55(1):18-25. Epub 2011/12/14.
152. Wald A, Bharucha AE, Cosman BC, Whitehead WE. ACG clinical guideline: management of benign anorectal disorders. The American journal of gastroenterology. 2014;109(8):1141-57; (Quiz) 058. Epub 2014/07/16.
153. Shatari T, Hayes J, Pretlove S, Toosz-Hobson P, Radley S, Keighley MR. Importance of evacuatory disturbance in evaluation of faecal incontinence after third degree obstetric tear. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2005;7(1):18-21. Epub 2004/12/21.
154. Miner PB, Jr. Economic and personal impact of fecal and urinary incontinence. Gastroenterology. 2004;126(1 Suppl 1):S8-13. Epub 2004/02/24.
155. Bharucha AE, Zinsmeister AR, Locke GR, Schleck C, McKeon K, Melton LJ. Symptoms and quality of life in community women with fecal incontinence. Clinical

gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2006;4(8):1004-9. Epub 2006/04/25.
156. Collings S, Norton C. Women's experiences of faecal incontinence: a study. British journal of community nursing. 2004;9(12):520-3. Epub 2005/01/19.
157. Damon H, Guye O, Seigneurin A, Long F, Sonko A, Faucheron JL, et al. Prevalence of anal incontinence in adults and impact on quality-of-life. Gastroenterologie clinique et biologique. 2006;30(1):37-43. Epub 2006/03/04.
158. Cotterill N, Norton C, Avery KN, Abrams P, Donovan JL. A patient-centered approach to developing a comprehensive symptom and quality of life assessment of anal incontinence. Diseases of the colon and rectum. 2008;51(1):82-7. Epub 2007/11/17.
159. Maeda Y, Vaizey CJ, Norton C. St. Mark's incontinence score. Diseases of the colon and rectum. 2007;50(12):2252. Epub 2007/09/28.
160. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Diseases of the colon and rectum. 1993;36(1):77-97. Epub 1993/01/01.
161. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Diseases of the colon and rectum. 2000;43(1):9-16; discussion -7. Epub 2000/05/17.
162. Bharucha AE, Zinsmeister AR, Locke GR, Seide BM, McKeon K, Schleck CD, et al. Prevalence and burden of fecal incontinence: a population-based study in women. Gastroenterology. 2005;129(1):42-9. Epub 2005/07/14.
163. Finne-Soveri H, Sorbye LW, Jonsson PV, Carpenter GI, Bernabei R. Increased work-load associated with faecal incontinence among home care patients in 11 European countries. European journal of public health. 2008;18(3):323-8. Epub 2007/09/04.
164. Mellgren A, Jensen LL, Zetterstrom JP, Wong WD, Hofmeister JH, Lowry AC. Long-term cost of fecal incontinence secondary to obstetric injuries. Diseases of the colon and rectum. 1999;42(7):857-65; discussion 65-7. Epub 1999/07/20.
165. Malouf AJ, Chambers MG, Kamm MA. Clinical and economic evaluation of surgical treatments for faecal incontinence. The British journal of surgery. 2001;88(8):1029-36. Epub 2001/08/08.
166. Abrams P, Cardozo L, Wein A. Fourth international consultation on incontinence-research society 2013. Neurourology and urodynamics. 2014;33(5):571-2. Epub 2014/06/20.
167. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology. 2006;130(5):1377-90. Epub 2006/05/09.
168. Faecal incontinence: The management of fecal incontinence in adults. GC49. London: National Institute for Health and Care Excellence. 2007.
169. Norton C, Whitehead WE, Bliss DZ, Harari D, Lang J, Conservative Management of Fecal Incontinence in Adults Committee of the International Consultation on I. Management of fecal incontinence in adults. Neurourology and urodynamics. 2010;29(1):199-206. Epub 2009/12/22.
170. Third- and Fourth-degree Perineal Tears, Management (Green-top Guideline No. 29). Royal College of Obstetricians and Gynaecologists; 2007.
171. Fernando RJ, Sultan AH, Kettle C, Thakar R. Methods of repair for obstetric anal sphincter injury. Cochrane database of systematic reviews. 2013;12:CD002866. Epub 2013/12/10.
172. MacArthur C, Bick DE, Keighley MR. Faecal incontinence after childbirth. British journal of obstetrics and gynaecology. 1997;104(1):46-50. Epub 1997/01/01.
173. Markland AD, Richter HE, Burgio KL, Myers DL, Hernandez AL, Subak LL. Weight loss improves fecal incontinence severity in overweight and obese women with

urinary incontinence. International urogynecology journal. 2011;22(9):1151-7. Epub 2011/05/14.
174. Burgio KL, Richter HE, Clements RH, Redden DT, Goode PS. Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. Obstetrics and gynecology. 2007;110(5):1034-40. Epub 2007/11/06.
175. Schnelle JF, Alessi CA, Simmons SF, Al-Samarrai NR, Beck JC, Ouslander JG. Translating clinical research into practice: a randomized controlled trial of exercise and incontinence care with nursing home residents. Journal of the American Geriatrics Society. 2002;50(9):1476-83. Epub 2002/10/18.
176. Norton C, Chelvanayagam S, Wilson-Barnett J, Redfern S, Kamm MA. Randomized controlled trial of biofeedback for fecal incontinence. Gastroenterology. 2003;125(5):1320-9. Epub 2003/11/05.
177. Bliss DZ, Jung HJ, Savik K, Lowry A, LeMoine M, Jensen L, et al. Supplementation with dietary fiber improves fecal incontinence. Nursing research. 2001;50(4):203-13. Epub 2001/08/02.
178. Omar MI, Alexander CE. Drug treatment for faecal incontinence in adults. Cochrane database of systematic reviews. 2013;6:CD002116. Epub 2013/06/13.
179. Read M, Read NW, Barber DC, Duthie HL. Effects of loperamide on anal sphincter function in patients complaining of chronic diarrhea with fecal incontinence and urgency. Digestive diseases and sciences. 1982;27(9):807-14. Epub 1982/09/01.
180. Engel BT, Nikoomanesh P, Schuster MM. Operant conditioning of rectosphincteric responses in the treatment of fecal incontinence. The New England journal of medicine. 1974;290(12):646-9. Epub 1974/03/21.
181. Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. Cochrane database of systematic reviews. 2012;7:CD002111. Epub 2012/07/13.
182. Oliveira L, Pfeifer J, Wexner SD. Physiological and clinical outcome of anterior sphincteroplasty. The British journal of surgery. 1996;83(4):502-5. Epub 1996/04/01.
183. Van Koughnett JA, Wexner SD. Current management of fecal incontinence: choosing amongst treatment options to optimize outcomes. World journal of gastroenterology : WJG. 2013;19(48):9216-30. Epub 2014/01/11.
184. Altomare DF, De Fazio M, Giuliani RT, Catalano G, Cuccia F. Sphincteroplasty for fecal incontinence in the era of sacral nerve modulation. World journal of gastroenterology : WJG. 2010;16(42):5267-71. Epub 2010/11/13.
185. Ruthmann O, Fischer A, Hopt UT, Schrag HJ. [Dynamic graciloplasty vs artificial bowel sphincter in the management of severe fecal incontinence]. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen. 2006;77(10):926-38. Epub 2006/08/10. Schliessmuskelprothese vs. Ersatzmuskelplastik bei hochgradiger Stuhlinkontinenz? Eine quantitative Analyse.
186. Brown SR, Wadhawan H, Nelson RL. Surgery for faecal incontinence in adults. Cochrane database of systematic reviews. 2013;7:CD001757. Epub 2013/07/04.
187. Madoff RD. Surgical treatment options for fecal incontinence. Gastroenterology. 2004;126(1 Suppl 1):S48-54. Epub 2004/02/24.
188. Ortiz H, Armendariz P, DeMiguel M, Solana A, Alos R, Roig JV. Prospective study of artificial anal sphincter and dynamic graciloplasty for severe anal incontinence. International journal of colorectal disease. 2003;18(4):349-54. Epub 2003/05/30.
189. Tan EK, Vaizey C, Cornish J, Darzi A, Tekkis PP. Surgical strategies for faecal incontinence--a decision analysis between dynamic graciloplasty, artificial bowel sphincter and end stoma. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2008;10(6):577-86. Epub 2007/11/17.
190. Tillin T, Gannon K, Feldman RA, Williams NS. Third-party prospective evaluation of patient outcomes after dynamic graciloplasty. The British journal of surgery. 2006;93(11):1402-10. Epub 2006/10/06.

191. Malone PS, Ransley PG, Kiely EM. Preliminary report: the antegrade continence enema. Lancet. 1990;336(8725):1217-8. Epub 1990/11/17.
192. Poirier M, Abcarian H, Nelson R. Malone antegrade continent enema: an alternative to resection in severe defecation disorders. Diseases of the colon and rectum. 2007;50(1):22-8. Epub 2006/11/23.
193. Lefevre JH, Parc Y, Giraudo G, Bell S, Parc R, Tiret E. Outcome of antegrade continence enema procedures for faecal incontinence in adults. The British journal of surgery. 2006;93(10):1265-9. Epub 2006/09/05.
194. Teichman JM, Zabihi N, Kraus SR, Harris JM, Barber DB. Long-term results for Malone antegrade continence enema for adults with neurogenic bowel disease. Urology. 2003;61(3):502-6. Epub 2003/03/18.
195. Takahashi-Monroy T, Morales M, Garcia-Osogobio S, Valdovinos MA, Belmonte C, Barreto C, et al. SECCA procedure for the treatment of fecal incontinence: results of five-year follow-up. Diseases of the colon and rectum. 2008;51(3):355-9. Epub 2008/01/22.
196. Abbas MA, Tam MS, Chun LJ. Radiofrequency treatment for fecal incontinence: is it effective long-term? Diseases of the colon and rectum. 2012;55(5):605-10. Epub 2012/04/20.
197. Maeda Y, Laurberg S, Norton C. Perianal injectable bulking agents as treatment for faecal incontinence in adults. Cochrane database of systematic reviews. 2013;2:CD007959. Epub 2013/03/02.
198. Graf W, Mellgren A, Matzel KE, Hull T, Johansson C, Bernstein M. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: a randomised, sham-controlled trial. Lancet. 2011;377(9770):997-1003. Epub 2011/03/23.
199. Wald A. New Treatments for Fecal Incontinence: Update for the Gastroenterologist. Clinical Gastroenterology & Hepatology. 2014;in press.
200. Mellgren A, Matzel KE, Pollack J, Hull T, Bernstein M, Graf W. Long-term efficacy of NASHA Dx injection therapy for treatment of fecal incontinence. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2014;26(8):1087-94. Epub 2014/05/20.
201. Colquhoun P, Kaiser R, Jr., Efron J, Weiss EG, Nogueras JJ, Vernava AM, 3rd, et al. Is the quality of life better in patients with colostomy than patients with fecal incontience? World journal of surgery. 2006;30(10):1925-8. Epub 2006/09/08.
202. Norton C, Burch J, Kamm MA. Patients' views of a colostomy for fecal incontinence. Diseases of the colon and rectum. 2005;48(5):1062-9. Epub 2005/05/04.
203. Thin NN, Horrocks EJ, Hotouras A, Palit S, Thaha MA, Chan CL, et al. Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. The British journal of surgery. 2013;100(11):1430-47. Epub 2013/09/17.
204. Jadav AM, Wadhawan H, Jones GL, Wheldon LW, Radley SC, Brown SR. Does sacral nerve stimulation improve global pelvic function in women? Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2013;15(7):848-57. Epub 2013/03/05.
205. Gallas S, Michot F, Faucheron JL, Meurette G, Lehur PA, Barth X, et al. Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: results of trial stimulation in 200 patients. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2011;13(6):689-96. Epub 2010/03/20.
206. Ratto C, Litta F, Parello A, Donisi L, De Simone V, Zaccone G. Sacral nerve stimulation in faecal incontinence associated with an anal sphincter lesion: a systematic review. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2012;14(6):e297-304. Epub 2012/02/24.

207. Boyle DJ, Knowles CH, Lunniss PJ, Scott SM, Williams NS, Gill KA. Efficacy of sacral nerve stimulation for fecal incontinence in patients with anal sphincter defects. Diseases of the colon and rectum. 2009;52(7):1234-9. Epub 2009/07/03.
208. Thin NN, Horrocks EJ, Hotouras A, Palit S, Thaha MA, Chan CLH, et al. Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. Brit J Surg. 2013;100(11):1430-47.
209. Leroi A-M, Parc Y, Lehur P-A, Mion F, Barth X, Rullier E, et al. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. Annals of surgery. 2005;242(5):662-9.
210. Dudding TC, Meng Lee E, Faiz O, Pares D, Vaizey CJ, McGuire A, et al. Economic evaluation of sacral nerve stimulation for faecal incontinence. The British journal of surgery. 2008;95(9):1155-63. Epub 2008/06/27.
211. Gladman MA, Knowles CH. Surgical treatment of patients with constipation and fecal incontinence. Gastroenterology clinics of North America. 2008;37(3):605-+.
212. Sprange K, Clift M, Burke M, Whitehead SR, Hutton J. Evidence Review: Sacral nerve stimulation for faeacl incontinence. Healthcare innovation and technology Evaluation Centre (HITEC). : Crown, 2009.
213. McGuire EJ, Zhang SC, Horwinski ER, Lytton B. Treatment of motor and sensory detrusor instability by electrical stimulation. The Journal of urology. 1983;129(1):78-9. Epub 1983/01/01.
214. Stoller ML. Afferent nerve stimulation for pelvic floor dysfunction. European urology. 1999;35:16.
215. Shafik A, Ahmed I, El-Sibai O, Mostafa RM. Percutaneous peripheral neuromodulation in the treatment of fecal incontinence. European surgical research Europaische chirurgische Forschung Recherches chirurgicales europeennes. 2003;35(2):103-7. Epub 2003/04/08.
216. Agur AMR, Dalley AF. Grant's atlas of anatomy. 12th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009. xvi, 864 p. p.
217. Carrington EV, Knowles CH. The influence of sacral nerve stimulation on anorectal dysfunction. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2011;13 Suppl 2:5-9. Epub 2011/02/10.
218. de la Portilla F, Rada R, Vega J, Gonzalez CA, Cisneros N, Maldonado VH. Evaluation of the use of posterior tibial nerve stimulation for the treatment of fecal incontinence: preliminary results of a prospective study. Diseases of the colon and rectum. 2009;52(8):1427-33. Epub 2009/07/21.
219. Vaizey CJ, Kamm MA, Turner IC, Nicholls RJ, Woloszko J. Effects of short term sacral nerve stimulation on anal and rectal function in patients with anal incontinence. Gut. 1999;44(3):407-12. Epub 1999/02/23.
220. Michelsen HB, Buntzen S, Krogh K, Laurberg S. Rectal volume tolerability and anal pressures in patients with fecal incontinence treated with sacral nerve stimulation. Diseases of the colon and rectum. 2006;49(7):1039-44. Epub 2006/05/25.
221. Rosen HR, Urbarz C, Holzer B, Novi G, Schiessel R. Sacral nerve stimulation as a treatment for fecal incontinence. Gastroenterology. 2001;121(3):536-41. Epub 2001/08/28.
222. Jarrett ME, Varma JS, Duthie GS, Nicholls RJ, Kamm MA. Sacral nerve stimulation for faecal incontinence in the UK. The British journal of surgery. 2004;91(6):755-61. Epub 2004/05/28.
223. Leroi AM, Parc Y, Lehur PA, Mion F, Barth X, Rullier E, et al. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. Annals of surgery. 2005;242(5):662-9. Epub 2005/10/26.
224. Boyle DJ, Prosser K, Allison ME, Williams NS, Chan CL. Percutaneous tibial nerve stimulation for the treatment of urge fecal incontinence. Diseases of the colon and rectum. 2010;53(4):432-7. Epub 2010/03/23.

225. George AT, Kalmar K, Sala S, Kopanakis K, Panarese A, Dudding TC, et al. Randomized controlled trial of percutaneous versus transcutaneous posterior tibial nerve stimulation in faecal incontinence. The British journal of surgery. 2013;100(3):330-8. Epub 2013/01/10.
226. Arroyo A, Parra P, Lopez A, Pena E, Ruiz-Tovar J, Benavides J, et al. Percutaneous posterior tibial nerve stimulation (PPTNS) in faecal incontinence associated with an anal sphincter lesion: results of a prospective study. International journal of surgery. 2014;12(2):146-9. Epub 2013/12/07.
227. de la Portilla F, Laporte M, Maestre MV, Diaz-Pavon JM, Gollonet JL, Palacios C, et al. Percutaneous neuromodulation of the posterior tibial nerve for the treatment of faecal incontinence - mid-term results: is retreatment required? Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2014;16(4):304-10. Epub 2014/03/13.
228. Lopez-Delgado A, Arroyo A, Ruiz-Tovar J, Alcaide MJ, Diez M, Moya P, et al. Effect on anal pressure of percutaneous posterior tibial nerve stimulation for faecal incontinence. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2014;16(7):533-7. Epub 2014/03/29.
229. Queralto M, Portier G, Cabarrot PH, Bonnaud G, Chotard JP, Nadrigny M, et al. Preliminary results of peripheral transcutaneous neuromodulation in the treatment of idiopathic fecal incontinence. International journal of colorectal disease. 2006;21(7):670-2. Epub 2005/12/07.
230. Leroi AM, Siproudhis L, Etienney I, Damon H, Zerbib F, Amarenco G, et al. Transcutaneous electrical tibial nerve stimulation in the treatment of fecal incontinence: a randomized trial (CONSORT 1a). The American journal of gastroenterology. 2012;107(12):1888-96. Epub 2012/10/04.
231. Griffin KM, Pickering M, O'Herlihy C, O'Connell PR, Jones JF. Sacral nerve stimulation increases activation of the primary somatosensory cortex by anal canal stimulation in an experimental model. The British journal of surgery. 2011;98(8):1160-9. Epub 2011/05/19.
232. Finazzi-Agro E, Rocchi C, Pachatz C, Petta F, Spera E, Mori F, et al. Percutaneous tibial nerve stimulation produces effects on brain activity: study on the modifications of the long latency somatosensory evoked potentials. Neurourology and urodynamics. 2009;28(4):320-4. Epub 2008/12/19.
233. Vodusek DB, Light JK, Libby JM. Detrusor Inhibition Induced by Stimulation of Pudendal Nerve Afferents. Neurourology and urodynamics. 1986;5(4):381-9.
234. Carrington EV, Evers J, Grossi U, Dinning PG, Scott SM, O'Connell PR, et al. A systematic review of sacral nerve stimulation mechanisms in the treatment of fecal incontinence and constipation. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2014;26(9):1222-37. Epub 2014/08/30.
235. Horrocks EJ, Thin N, Thaha MA, Taylor SJ, Norton C, Knowles CH. Systematic review of tibial nerve stimulation to treat faecal incontinence. The British journal of surgery. 2014;101(5):457-68. Epub 2014/01/22.
236. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700. Epub 2009/07/23.
237. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996;17(1):1-12. Epub 1996/02/01.
238. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928. Epub 2011/10/20.

239. Govaert B, Pares D, Delgado-Aros S, La Torre F, Van Gemert WG, Baeten CG. A prospective multicentre study to investigate percutaneous tibial nerve stimulation for the treatment of faecal incontinence. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2010;12(12):1236-41. Epub 2009/08/14.
240. Findlay JM, Yeung JM, Robinson R, Greaves H, Maxwell-Armstrong C. Peripheral neuromodulation via posterior tibial nerve stimulation - a potential treatment for faecal incontinence? Annals of the Royal College of Surgeons of England. 2010;92(5):385-90. Epub 2010/07/16.
241. Hotouras A, Thaha MA, Allison ME, Currie A, Scott SM, Chan CL. Percutaneous tibial nerve stimulation (PTNS) in females with faecal incontinence: the impact of sphincter morphology and rectal sensation on the clinical outcome. International journal of colorectal disease. 2012;27(7):927-30. Epub 2012/01/26.
242. Hotouras A, Murphy J, Walsh U, Allison M, Curry A, Williams NS, et al. Outcome of percutaneous tibial nerve stimulation (PTNS) for fecal incontinence: a prospective cohort study. Ann Surg. 2014;259(5):939-43. Epub 2013/08/28.
243. Al Asari S, Meurette G, Mantoo S, Kubis C, Wyart V, Lehur PA. Percutaneous tibial nerve stimulation vs sacral nerve stimulation for faecal incontinence: a comparative case-matched study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2014;16(11):O393-9. Epub 2014/06/10.
244. Hotouras A, Murphy J, Allison M, Curry A, Williams NS, Knowles CH, et al. Prospective clinical audit of two neuromodulatory treatments for fecal incontinence: sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS). Surgery today. 2014;44(11):2124-30. Epub 2014/05/06.
245. Vitton V, Damon H, Roman S, Mion F. Transcutaneous electrical posterior tibial nerve stimulation for faecal incontinence: effects on symptoms and quality of life. International journal of colorectal disease. 2010;25(8):1017-20. Epub 2010/06/05.
246. Vitton V, Damon H, Roman S, Nancey S, Flourie B, Mion F. Transcutaneous posterior tibial nerve stimulation for fecal incontinence in inflammatory bowel disease patients: a therapeutic option? Inflammatory bowel diseases. 2009;15(3):402-5. Epub 2008/10/31.
247. Eleouet M, Siproudhis L, Guillou N, Le Couedic J, Bouguen G, Bretagne JF. Chronic posterior tibial nerve transcutaneous electrical nerve stimulation (TENS) to treat fecal incontinence (FI). International journal of colorectal disease. 2010;25(9):1127-32. Epub 2010/06/16.
248. Thomas GP, Dudding TC, Nicholls RJ, Vaizey CJ. Bilateral transcutaneous posterior tibial nerve stimulation for the treatment of fecal incontinence. Diseases of the colon and rectum. 2013;56(9):1075-9. Epub 2013/08/10.
249. Thomas GP, Dudding TC, Bradshaw E, Nicholls RJ, Vaizey CJ. A pilot study to compare daily with twice weekly transcutaneous posterior tibial nerve stimulation for faecal incontinence. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2013;15(12):1504-9. Epub 2013/10/15.
250. Hotouras A, Thaha MA, Allison ME, Currie A, Scott SM, Chan CL. Percutaneous tibial nerve stimulation (PTNS) in females with faecal incontinence: the impact of sphincter morphology and rectal sensation on the clinical outcome. International journal of colorectal disease. 2012. Epub 2012/01/26.
251. Hotouras A, Thaha MA, Boyle D, Allison ME, Currie A, Knowles CH, et al. Short-term outcome following percutaneous tibial nerve stimulation (PTNS) for faecal incontinence: a single-centre prospective study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2011. Epub 2011/12/08.

252. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut. 1999;44(1):77-80. Epub 1998/12/24.
253. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. The British journal of surgery. 1995;82(2):216-22. Epub 1995/02/01.
254. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988;26(7):724-35. Epub 1988/07/01.
255. Group E. Available from: http://www.euroqol.org/.
256. Cotterill N, Norton C, Avery KN, Abrams P, Donovan JL. Psychometric evaluation of a new patient-completed questionnaire for evaluating anal incontinence symptoms and impact on quality of life: the ICIQ-B. Diseases of the colon and rectum. 2011;54(10):1235-50. Epub 2011/09/10.
257. Peters KM, Carrico DJ, Perez-Marrero RA, Khan AU, Wooldridge LS, Davis GL, et al. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. The Journal of urology. 2010;183(4):1438-43. Epub 2010/02/23.
258. Allison M. Percutaneous tibial nerve stimulation: a new treatment for faecal incontinence. . Gastrointestinal Nursing 2009;7:22-9.
259. Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. The American journal of medicine. 1999;107(5A):91S-7S. Epub 1999/12/10.
260. Musial F, Klosterhalfen S, Enck P. Placebo responses in patients with gastrointestinal disorders. World journal of gastroenterology : WJG. 2007;13(25):3425-9. Epub 2007/07/31.
261. Ilnyckyj A, Shanahan F, Anton PA, Cheang M, Bernstein CN. Quantification of the placebo response in ulcerative colitis. Gastroenterology. 1997;112(6):1854-8. Epub 1997/06/01.
262. Goldstein H. REAL COM-IMPUTE software for multilevel multiple imputation with mized response types. . Journal of Statistical Software.45(5):1-12.
263. Kahan BC, Morris TP. Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects? Statistics in medicine. 2013;32(7):1136-49. Epub 2012/11/01.
264. Cotterill N, Norton C, Avery KNL, Abrams P, Donovan JL. Psychometric Evaluation of a New Patient-Completed Questionnaire for Evaluating Anal Incontinence Symptoms and Impact on Quality of Life: The ICIQ-B. Diseases of the Colon & Rectum. 2011;54(10):1235-50.
265. Asari SA, Meurette G, Mantoo S, Kubis C, Wyart V, Lehur PA. Percutaneous tibial nerve versus sacral nerve stimulation for faecal incontinence: a comparative case-matched study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2014. Epub 2014/06/10.
266. Hotouras A, Murphy J, Allison M, Curry A, Williams NS, Knowles CH, et al. Prospective clinical audit of two neuromodulatory treatments for fecal incontinence: sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS). Surgery today. 2014. Epub 2014/05/06.
267. Thin NN, Taylor SJ, Bremner SA, Emmanuel AV, Hounsome N, Williams NS, et al. Randomized clinical trial of sacral versus percutaneous tibial nerve stimulation in patients with faecal incontinence. The British journal of surgery. 2015;102(4):349-58. Epub 2015/02/04.
268. Finazzi-Agro E, Petta F, Sciobica F, Pasqualetti P, Musco S, Bove P. Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a

placebo effect: a randomized, double-blind, placebo controlled trial. The Journal of urology. 2010;184(5):2001-6. Epub 2010/09/21.
269. Vaizey CJ. Faecal incontinence: standardizing outcome measures. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2014;16(3):156-8. Epub 2014/01/24.
270. Graf W, Mellgren A, Matzel KE, Hull T, Johansson C, Bernstein M, et al. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: a randomised, sham-controlled trial. Lancet. 2011;377(9770):997-1003. Epub 2011/03/23.
271. Wexner SD, Coller JA, Devroede G, Hull T, McCallum R, Chan M, et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multicenter study. Ann Surg. 2010;251(3):441-9. Epub 2010/02/18.
272. Pacheco-Lopez G, Engler H, Niemi MB, Schedlowski M. Expectations and associations that heal: Immunomodulatory placebo effects and its neurobiology. Brain, behavior, and immunity. 2006;20(5):430-46. Epub 2006/08/05.
273. Mearin F, Balboa A, Zarate N, Cucala M, Malagelada JR. Placebo in functional dyspepsia: symptomatic, gastrointestinal motor, and gastric sensorial responses. The American journal of gastroenterology. 1999;94(1):116-25. Epub 1999/02/06.
274. Allescher HD, Bockenhoff A, Knapp G, Wienbeck M, Hartung J. Treatment of non-ulcer dyspepsia: a meta-analysis of placebo-controlled prospective studies. Scandinavian journal of gastroenterology. 2001;36(9):934-41. Epub 2001/08/28.
275. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. Alimentary pharmacology & therapeutics. 2001;15(3):355-61. Epub 2001/02/24.
276. Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2003;15(1):79-86. Epub 2003/02/18.
277. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. Archives of internal medicine. 2003;163(3):265-74. Epub 2003/02/13.
278. Howick JC, I. Glasziou, P. Greenhalgh, T. Heneghan, C. Liberati, A. Moschetti, I. Phillips, B. Thornton, H. . The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document). Oxford Centre for Evidence-Based Medicine2011; Available from: http://www.cebm.net/index.aspx?o=5653.
279. Dinning PG, Hunt L, Patton V, Zhang T, Szczesniak M, Gebski V, et al. Treatment efficacy of sacral nerve stimulation in slow transit constipation: a two-phase, double-blind randomized controlled crossover study. The American journal of gastroenterology. 2015;110(5):733-40. Epub 2015/04/22.
280. Beecher HK. The powerful placebo. Journal of the American Medical Association. 1955;159(17):1602-6. Epub 1955/12/24.
281. Kienle GS, Kiene H. The Powerful Placebo Effect: Fact or Fiction? Journal of Clinical Epidemiology. 1997;50(12):1311-8.
282. Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. Cochrane database of systematic reviews. 2010(1):CD003974. Epub 2010/01/22.
283. Enck P, Horing B, Weimer K, Klosterhalfen S. Placebo responses and placebo effects in functional bowel disorders. European journal of gastroenterology & hepatology. 2012;24(1):1-8. Epub 2011/09/15.
284. Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. Lancet. 1995;346(8984):1231. Epub 1995/11/04.
285. Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? Nature reviews Neuroscience. 2005;6(7):545-52. Epub 2005/07/05.

286. Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. Evaluation & the health professions. 2005;28(1):9-26. Epub 2005/01/29.
287. NICE Guidelines for Faecal Incontinence. May 2011; Available from: http://www.nice.org.uk/CG49.
288. Hodgekiss A. Me and my operation: How a tiny needle in your ankle stops those urgent trips to the loo. Daily Mail. 2013 27th August 2013.
289. Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. Best practice & research Clinical gastroenterology. 2011;25(1):29-41. Epub 2011/03/09.
290. Collins B, Norton C, Maeda Y. Percutaneous tibial nerve stimulation for slow transit constipation: a pilot study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2012;14(4):e165-70. Epub 2011/09/14.
291. Whitehead WEC, S.; Corazziari, E.; Kumar, D. Report of an international workshop on management of constipation. Gastroenterology Int. 1991;4:99-113.
292. Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated patients. Diseases of the colon and rectum. 1996;39(6):681-5. Epub 1996/06/01.
293. Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. Best Pract Res Clin Gastroenterol. 2011;25(1):29-41. doi: 10.1016/j.bpg.2010.12.002.
294. Burgell RE, Bhan C, Lunniss PJ, Scott SM. Fecal incontinence in men: coexistent constipation and impact of rectal hyposensitivity. Dis Colon Rectum. 2012;55(1):18-25. doi: 10.1097/DCR.0b013e318237f37d.

9 Appendices

9.1 Appendix 1: Bowel Diary

Day	1	2	3	4	5	6	7
Controlled bowel movements (no incontinence: underwear, pads or pants remained clean)							
How many times did you go to the toilet (controlled)?							
Uncontrolled bowel movements (incontinence: underwear, pads or pants got dirty)							
How many times did you NOT make it in time to toilet (rush)?							
How many times did you not feel the bowel movement but only afterwards (passive leakage)?							
Staining/ minor soiling of underwear							
Did you stain/soil your underwear, pants or pad(s) today?	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no
Pad usage/Enema/ Suppository							
Pad(s) used for incontinence?	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no
Enema Suppository administrated?	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no
Social functioning							
Did your (faecal) incontinence limit you in your daily activities (e.g. leaving the house, shopping etc)?	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no
Stool consistency							
What was your stool consistency today? (Circle one)	Solid/ mushy/ liquid	Solid/ mushy/ liquid	Solid/ mushy/ liquid	Solid/ mushy/ liquid	Solid/ mushy/ liquid	Solid/ mushy/ liquid	Solid/ mushy/ liquid

9.2 Appendix 2: St Marks' Continence Score

	Never	Rarely	Sometimes	Weekly	Daily
How often do you have incontinence (accidents) with solid stool?					
How often do you have incontinence (accidents) with liquid stool?					
How often do you lose control of gas/wind?					
How often do your bowel symptoms affect your lifestyle?					
				No	Yes
Do you use a Pad or anal plug?					
Do you medications to make that make you constipated?					
Do you have to rush to the toilet as soon as you have an urge to go?					

9.3 Appendix 3: Cleveland Clinic Incontinence Score

Cleveland Clinic Incontinence Score

Please tick one box in each row to indicate on average how often you experience the following:

	Never	**Rarely** Less than once a month	**Sometimes** Less than once a week	**Usually** Less than once a day	**Always** Everyday
a. Solid stool leakage	☐	☐	☐	☐	☐
b. Liquid stool leakage	☐	☐	☐	☐	☐
c. Gas leakage	☐	☐	☐	☐	☐
d. Pad use (for stool)	☐	☐	☐	☐	☐
e. Lifestyle restriction	☐	☐	☐	☐	☐

9.4 Appendix 4: Supplementary tables for systematic review

Table 39: Other outcomes in randomised trials of percutaneous and transcutaneous tibial nerve stimulation

Reference	Outcome	Results
Leroi *et al.* (2012)	FIQL score	No significant differences between the two groups*
	Patient-perceived success	No difference in patient-perceived treatment efficacy between groups: TTNS 30% (0–100) vs. sham 20% (0–100) success (P = 0.024)
	Physician-perceived success	Physician-estimated treatment efficacy significantly higher in TTNS group: TTNS 59% vs. sham 35% improved (P = 0.01)
	Anorectal manometry	No significant difference between two groups in anorectal manometry at 3 months compared with baseline
George *et al.* (2013)	St Mark's incontinence score	All groups demonstrated improvement in incontinence score, but no significant difference between groups (P = 0.201)
	FIQL score	All groups demonstrated improvement in FIQL score, but no significant difference between groups in any domain
	SF-36® QoL score	All groups demonstrated improvement in SF-36® score, but significant difference between groups only in vitality domain (P = 0.008)
	Anorectal manometry	No anorectal physiology assessments showed any significant difference between groups
Thomas *et al.* (2013)	St Mark's incontinence score	No comparison made between groups
	Percentage reduction in weekly FIE	No comparison made between groups
	Weekly frequency of defaecation	No comparison made between groups
	Ability to defer defaecation	No comparison made between groups
	FIQL Score	No comparison made between groups
	SF-36® QoL score	No comparison made between groups
	Time taken to return to baseline FI episodes	No comparison made between groups

*In terms of median relative changes compared with baseline. FIQL, Faecal Incontinence Quality of Life Scale; TTNS, transcutaneous tibial nerve stimulation; SF-36®, Short Form 36 (QualityMetric, Lincoln, Rhode Island, USA).

Table 40: Characteristics of RCTs (publication order)

Study	Characteristic	Description
Leroi *et al*. 2012	Methods	Study Design: Multi-centre double-blind randomised sham-controlled trial. Follow-up: 3 months after treatment commencement i.e. immediately after cessation of treatment. Total study duration: 4 months.
	Participants	144 patients selected from consecutive patients referred for FI to the nine centres. (F=131, M=13). Age 30-82 years. Inclusion criteria: FI lasting > 3 months, with FI defined as more than one incontinent episode (or urgency episode causing the patient to remain at home to avoid incontinent episode) on average per week; failure of conservative treatments; not a candidate for conservative treatments and ≥ 18 years of age. Exclusion criteria: Congenital anorectal malformation; previous colorectal resection; pelvic irradiation; rectal prolapse; faecal impaction; external anal sphincter defect exceeding 90 degrees in circumference; implanted pacemaker or defibrillator; pregnant or intention to become pregnant; complete peripheral or central neurological lesion; rapidly progressive neurological disease (in <6 months); anatomical limitations preventing the successful placement of an electrode; previous experience with therapeutic electrical stimulation such that the patient did not suspect that he or she was being treated with a sham stimulation; and chronic diarrhoea resistant to medical treatment. TTNS Group: n=73 (M=5, F=68). Median age 60 years (range: 30-80 years). Median duration of symptoms 5 years (range: 1–36 years). Sham group: n=71 (M=8, F=63). Median age 59.3 years (range: not reported). Median duration of symptoms 8.8 years (range: not reported). Groups similar with no significant difference in sex, age and duration of symptoms.
	Interventions	Randomisation performed using a random number table stratified based on the CCIS score. No other details given. Intervention Group: Electrical stimulation performed with TENS Eco Program P3 stimulator applied over tibial nerve using method described by Qualtero *et al.* Negative electrode behind internal mallelous positive electrode 10cm above negative electrode. Correct position of negative electrode detrmined by observing rhythmc flexing of toes. Intensity level set just under threshold causing motor contraction. Stimulation applied in continuous mode at 10Hz with a 200 μs pulse width. Patients shown how to operate stimulator and requested to perform 20-minute stimulation sessions twice daily for 3 months at home. Sham group: Equipment set up identically to treatment group. Sham stimulations performed with a placebo stimulator that physically resembled the active stimulator but did not deliver a current. Patients were shown how to operate stimulator and requested to

		perform 20-minute stimulation sessions twice daily for 3 months at home.
	Outcomes	Bowel diaries regarding episodes of FI and urgency for 3 weeks prior to treatment and throughout the 3 month treatment duration. CCIS at baseline and following 3 months treatment. Delay in postponing defaecation at baseline and following 3 months treatment. FIQL at baseline and following 3 months treatment. Patients opinion regarding efficacy of the treatment using graduated 100mm vertical line ranging from "0 = no efficacy at all" to "100 = complete efficacy with cure". Evaluating physician also asked whether they felt treatment was effective or not. Anal manometry at baseline and after 3 months treatment.
George *et al.* 2013	Methods	Study Design: Single centre single blind randomised controlled trial with 3 arms. Group 1: Percutaneous tibial nerve stimulation Group 2: Transcutaneous tibial nerve stimulation Group 3: Sham transcutaneous tibial nerve stimulation Follow-up: 6 months. Total study duration: 8 months.
	Participants	Thirty patients recruited into 3 arms of study. Inclusion criteria: Age>18 years with at least two or more episodes of FI per week. Exclusion criteria: Previous congenital or acquired spinal injury, spinal tumour or spinal surgery, presence of neurological diseases (such as diabetic neuropathy, multiple sclerosis and Parkinson's disease), peripheral vascular disease, uncontrolled diabetes mellitus, congenital anorectal malformations, recent rectal surgery (rectopexy or resection within 24 months), presence of external full-thickness rectal prolapse, inflammatory bowel disease, chronic diarrhoea uncontrolled by drugs or diet, previous use of tibial nerve stimulation, stoma *in situ*, bleeding complications, and pregnancy or attempting to conceive. Group 1: n=11. Sex not stated. Age not stated. Group 2: n=11. Sex not stated. Age not stated. Group 3: n=8. Sex not stated. Age not stated. No comment on similarities between groups.
	Interventions	Randomisation via sealed-envelope technique. Group 1: PTNS using Uroplasty Urgent PC on either leg. Current increased until both motor and sensory responses noticable. Current set at the highest level tolerable by patient. Patients treated with twice-weekly 30-minute sessions for 6 weeks. Group 2: Using the NeuroTrac Continence Neurostimulator by Premiere Medical Products. Two self-adhesive surface electrodes

		placed with the negative behind the medial malleolus and the positive 10cm above it. Current increased until motor and sensory responses obtained. Current at the highest level tolerable to patient. Stimulation was given in twice-weekly 30-minute sessions for 6 weeks. Group 3: Using same equipment as described for group 2. Equipment set up as above but stimulator only briefly switched on for 30 seconds to induce a minor electrical sensation in the skin and then turned off for the remaining treatment duration. Patients attended for twice-weekly 30-minute sessions for 6 weeks.
	Outcomes	Bowel diaries recording weekly episodes of faecal incontinence, St Mark's Continence Score, Rockwood Quality of Life Score and SF-36 Quality of Life score were recorded before and after treatment.
Thomas *et al.* 2013	Methods	Study design: Single-centre single blind (assessor only) randomised study to compare daily with twice-weekly transcutaneous tibial nerve stimulation. Follow-up: 6 weeks after commencement of treatment, i.e. immediately after cessation of treatment.
	Participants	29 patients from a single centre (from 30 originally recruited). 26 females. Inclusion criteria: Signed consent form; 18-80 years of age; FI defined as at least 2 episodes per week of involuntary loss of either liquid or solid stool; previous unsuccessful biofeedback; willingness to attend for the study; willing and able to complete the questionnaires and bowel diaries; no previous neuromodulation. Exclusion criteria: Congenital or acquired spinal injury, tumour or surgery; peripheral vascular disease; peripheral neuropathy or neurological disorder; anorectal surgery within the last year; full thickness rectal prolapse; active inflammatory bowel disease; psychological or physical inability to cope with the study protocol; pregnancy or attempting to become pregnant. Daily TTNS: 14 patients (all female). Median age 54.5 IQR (8.5) years. Median duration of symptoms 6 years (IQR 4.13). Weekly TTNS: 15 patients (12 females). Median age 51 IQR (29) years. Median duration of symptoms 5 years (IQR 9).
	Interventions	Randomisation, performed by a third party who did not take part in analysis of results, was by random selection of a sealed opaque envelope, which contained group allocation. No other details given. Treatment: All patients performed treatments at home for 6 weeks following one to one instruction on the use of TTNS, written instructions and a photograph demonstrating the electrode pad and lead position. TTNS was given using a NeuroTrac TENS transcutaneous electrical nerve stimulator (Verity medical Ltd, Hampshire, UK) via two 50 mm x 50 mm electrode pads. The live pad was placed posterior and superior to the medial malleolus and the ground pad was placed 10cm cephalad to this. Continuous stimulation at pulse width 200 microseconds and frequency 10Hz was used. Amplitude was set to produce a sensory stimulus in the

		ipsilateral foot, at a tolerable intensity. All treatments were given for 30 minutes. Twice weekly: Patients randomised to this group self-treated at home twice weekly. Daily: Patients randomised to this group self-treated at home daily.
	Outcomes	Primary outcome: Frequency of faecal incontinence episodes per week. These were measured from 2-week bowel diaries before and after treatment. Secondary outcomes: Ability to defer defaecation (measured in minutes), the frequency of defaecation, changes in St Marks Continence Score and changes in FIQL score. The SF-36 survey was also conducted and a visual analogue scale assessing patient response to 'how happy are you with the way your bowels have been functioning' on a scale of 0 (very unhappy) to 100 (very happy). All outcomes were assessed prior to and immediately following a 6-week course of treatment in both arms.

Table 41: Other outcomes in studies of percutaneous tibial nerve stimulation

Reference	Outcome	Results
Shafik *et al*. (2003)	Rectometrogram	No clear result shown
	Recurrence of symptoms	Recurrence of symptoms in 30% patients who originally had success, and with further treatment 75% had improved symptoms again
De la Portilla *et al*. (2009)	FIQL score	FI no longer affected QoL 6 months after treatment in 12.5% patients (reduction from 37.5% of patients to 25%)
		Significant improvement in FIQL score in depression, coping/behaviour and embarrassment domains, but not in lifestyle 6 months after treatment *versus* baseline ($P < 0.004$, $P < 0.02$, $P < 0.005$ and $P = 0.086$ respectively)*
	VAS for QoL	Significant improvement at 3 months and after 6 months without treatment ($P = 0.002$ and $P = 0.001$ respectively)*
	Anorectal manometry	Significant improvement found in mean squeeze pressure between baseline and 6 months after treatment ($P < 0.007$), but not in resting pressures or rectal sensation
Govaert *et al*. (2009)	SF-36®	SF-36® improved significantly in all domains apart from vitality at 1 year ($P < 0.005$)*
	FIQL score	FIQL improved significantly in coping/behaviour and embarrassment domains after treatment, and in lifestyle and coping/behaviour domains at 1 year ($P < 0.005$)*
Boyle *et al*. (2010)	Time to defer defaecation	Deferment of defaecation time improved in 65% patients from a median of 1 (range 0–15) to 5 (0–25) min ($P < 0.001$)
	Duration of effect	Duration of effect data not collected or reported systematically
	Outcome *versus* physiological parameters	No correlation found between outcome and physiological parameters
Findlay *et al*. (2010)	HAD score	Significant improvements seen in ICIQ-B score bowel control and quality of life domains ($P = 0.001$ and $P = 0.007$ respectively), and in FIQL score lifestyle domain ($P = 0.028$)*. All other parameters showed non-significant improvements
	ICIQ-B score	
	FIQL score	
Hotouras *et al*. (2012)	Time to defer defaecation	Improved significantly from 1 (range 0–30) min before treatment to 5 (0–60) min after treatment ($P < 0.001$)
George *et al*. (2012)	St Mark's incontinence score	Improvement in continence score seen, but no comment on significance*
	FIQL score	Improvement in FIQL score, but no comment on significance*
	SF-36® QoL score	Improvement in SF-36® score, but no comment on significance*
	Anorectal manometry	Significant improvement in mean peak squeeze pressure from baseline to post-treatment from mean (s.d.) 50(29) to 68(34) cmH2O (P = 0.043)
Arryo *et al.*(2014)	VAS for faecal incontinence	Significant improvement from baseline 6 to 7.5 at 6 months (p=0.001)
	Time to defer defaecation	Improvement from 2 minutes at baseline to 4 minutes at 6 months (p=0.008)
	Anal manometry	Significant improvement in maximum resting pressure from 41 ± 26 mmHg to 51 ± 31 mmHg (p<0.001) at 6 months and in maximum squeeze pressure from 83 ± 35 mmHg to 94 ± 52 mmHg

		(p<0.001)
Al Asari *et al.* (2014)	FIQL score	Significant improvement in score from baseline to 6 months (mean 2.1 to 3.1, p<0.001) and baseline to 12 months (mean 2.1 to mean 3.1, p<0.001)
	PTNS vs. SNS	No difference in proportion of patients achieving >50% improvement in CCIS between PTNS and SNS at 6 months or 12 months. 6 months 47% vs. 50% (p=0.53). 12 months 30.7% vs. 57.5% (p=0.09). No significant difference in FIQL score at baseline between groups. No significant difference in FIQL score between PTNS and SNS groups at 6 months (p=0.79) or 12 months (0=0.37).
Hotouras *et al.*(2014)	Time to defer defaecation	Improved from median of 1 minute (range 0-60 minutes) to 5 minutes (range 0-60).
	PTNS vs. SNS in 'pseudo' case-control model	Significantly more incontinence episodes in SNS group prior to treatment (p=0.02). No significant difference in incontinence episodes between groups following treatment (0.27). No significant difference in deferment time between groups.
De la Portilla *et al.*(2014)	VAS for QOL	Improved significantly from mean (s.d.) 15 (±3.6) to 10 (±5.6) after treatment (p=0.005), 9 (±6) after 9 months (p=0.005) and 8.6 (±6) after 27 months (p=0.001)
	FIQL score	Significant improvement at 27 months from baseline in three of the four domains; lifestyle (p=0.013), behaviour (p=0.005) and embarrassment (p=0.002)
	Anorectal manometry	Significant improvement in squeeze pressure (p=0.019) and threshold volume for desire to defaecate (p=0.043) at 27 months compared to baseline
Hotouras *et al*. (2014)	Time to defer defaecation	Significantly improved from a median of 1 minute to 5 minutes at 3 months (p<0.001) and from a median of 1 minute to 4 minutes after a median of 29 months follow up (0<0.001).
	Univariate and multivariate analysis	No effect of age, sex, incontinence type, intact IAS, intact EAS, anal resting and squeeze pressures on mean reduction in CCIS.
	FIQL	A significant improvement from baseline to both follow-up periods (3 months and median 29 months) in all domains; lifestyle, coping, depression and embarrassment.
Lopez-Delgado *et al.*(2014)	Time to defer defaecation	At baseline 75% patients had urgency <1 minute. This fell to 12.5% by 3 months and to 0% at 6 months. At 6 months 75% patients had urgency of 1-5 minutes. No statistical analysis performed.
	VAS of perception of degree of incontinence.	VAS for perception of degree of incontinence improved from 2.5 to 2.4 however this was not statistically significant.
	FIQL	There were no differences in the domains of FIQL score before and after 3 or 6 months treatment. No raw data or analysis shown.
	Incontinence episodes	Incontinence diaries showed a 'slight improvement' with a trend towards improvements in patients with between three and seven episodes per week at 6 months, however this was not statistically significant.
	Associations	A frequency of incontinent episodes of <3 per week was associated with a better response to PTNS (OR=2, 95% CI 1-3.97; P=0.027). Previous episiotomy and baseline CCIS>12 were negative predictors of response to PTNS (OR=5.78, 95% CI 1.77-21.53; P=0.007) and (OR=2.9, 95% CI 1.09-6.72; P-0.035).

	Anal manometry	When patients with negative outcome were excluded, significant improvements in mean resting pressure and mean squeeze pressures were seen at 3 months (p=0.043 and p=0.049 respectively) and at 6 months (p=0.021 and p=0.045 respectively). Significant inverse correlations were seen at 6 months between CCIS and both mean resting and mean squeeze pressures.

*Mean values reported in study. FIQL, Faecal Incontinence Quality of Life Scale; QoL, quality of life; VAS, visual analogue scale; SF-36®, Short Form 36 (QualityMetric, Lincoln, Rhode Island, USA); HAD, Hospital Anxiety and Depression Scale; ICIQ-B, International Consultation on Incontinence Questionnaire – Bowel module.

Table 42: Characteristics of PTNS studies (publication order)

Study	Characteristic	Description
Shafik *et al.* 2003	Methods	Study design: Non-randomised prospective case series with control group. Study duration: 4 weeks. Follow-up: 16-30 months (mean 22.3 months +/-4.6).
	Participants	32 patients with idiopathic FI (M=10, F=22) Intervention group: Mean age 38.2 +/- 6.7 years. Mean duration FI 8.6 +/- 2.7 years. "Control" group: 'Twenty patients with FI who matched the treated group in age, duration of symptoms and investigative results acted as controls.' F=14; M=6. Inclusion: FI (incontinent of solid stools) with normal EMG activity of EAS, puborectalis and levator ani and normal anorectal sensitivity, anal pressure, defecography and endoanal USS. Failure of medical therapies, pelvic floor stimulation, Kegel exercise and biofeedback. Exclusion: Not mentioned
	Interventions	Intervention group: PTNS using Stoller Afferent Nerve Stimulator. Unilateral stimulation. Parameter recognised by flexion of big or other toes. 30-minute stimulations every other day for 4 weeks (14 treatments). In case of symptom recurrence, stimulation repeated twice per week for 4 weeks. Control group: Equipment attached but no stimulation given.
	Outcomes	Bowel incontinence questionnaire (Solid, liquid and flatus incontinence, pad usage, daily social functioning) Rectometrogram measuring rectal volume, pressure and compliance at the first rectal and urge sensation (twice in each patient to ensure reproducibility)
De la Portilla *et al.* 2009	Methods	Study Design: Non-randomised prospective case series. Follow-up: Immediately after 3-months treatment. Those with treatment success continued therapy and were followed up until 6 months after treatment cessation. Total study duration: 14 months.
	Participants	Sixteen patients (11 female) mean age 59 +/- 7.9 years. Inclusion criteria: Age 18-80, CCIS score 10 or higher, >4 fecal leaks within 28 days as well as duration >6 months, failure of conservative treatment and integrity of external anal sphincter. Exclusion criteria: severe cardiopulmonary disease, lesion of the tibial nerve, severe distal venous insufficiency, cardiac pacemaker or implantable defibrillator, inflammatory bowel disease,

		uncontrolled diabetes with peripheral nerve involvement, immunosuppression, active anal fissure, fistula or abscess, or pregnancy.
	Interventions	PTNS using Uroplasty Urgent PC. Amplitude increased until plantarflexion or fanning of toes and kept at level where sensation was available. 30 minute stimulations weekly for 12 weeks. If good response achieved (CCIS score decrease to <40% of original score) treatment continued at every two weeks for 2 months, every three weeks for 2 months and then a final treatment a month later. Total 20 treatments.
	Outcomes	CCIS score and FIQL questionnaire at all time-points (before treatment; after 3 months treatment; after 8 months treatment and after 6 months without treatment). Visual analogue scale of success before treatment and after 3 months initial treatment. Bowel diary before treatment, after 8 months treatment and after 6 months without treatment.
Govaert *et al.* 2009	Methods	Study Design: Multicentre non-randomised prospective case series. Follow-up: Immediately after 6-weeks treatment. Those with treatment success continued therapy and were followed up at 3 months, 6 months and 1 year. Total study duration: 12 months.
	Participants	22 patients (16 female) mean age 60.4 +\-11.7 years. Inclusion criteria: Age>/= 18, FI with solid or liquid stool causing disruption to lifestyle, psychological stability and suitability for intervention as determined by the investigator, willing to commit to a rigid follow-up schedule, failed conservative therapy, intact peripheral neurosensory nervous system as determined by clinical investigation, adequate motor and/or sensory response during treatment, able to read and write. Exclusion Criteria: Major internal or external anal sphincter defect (>120 degrees of circumference), faecal impaction, implanted pacemaker, defibrillator, cardiopathy or bleeding disorder, pregnancy or intention to become pregnant, neurogenic or congential disorders resulting in fecal incontinence (multiple sclerosis and spina bifida) unable to travel to the hospital to receive the treatment.
	Interventions	PTNS using Uroplasty Urgent PC on either leg. Amplitude increased until sensory and/or motor responses were evident. 30 minute stimulations twice weekly for 6 weeks. If patients had sufficient subjective reduction in symptoms, maintanence therapy was started. This consisted of weekly sessions for 6 weeks, fortnightly sessions for 8 weeks and monthly sessions for 6 months. Total treatment duration: 11 months.
	Outcomes	CCIS at all time-points (before treatment; after 6-weeks, 3-months, 6-months and 1-year). Bowel diaries at baseline, after 6 weeks treatment and after 1 year. SF-36 and FIQL questionnaires at baseline and after 6 weeks

		treatment.
Boyle *et al.* 2010	Methods	Study Design: Single centre non-randomised prospective case series. Follow-up: Median 9 months (range 3-14 months).
	Participants	33 patients (32 female) median age 58 (range 34-77). Inclusion criteria: All patients referred for conservative management of urge FI. Exclusion criteria: Pregnancy or intended pregnancy, implanted pacemaker or defibrillator, history of ischemic heart disease, peripheral neuropathy, any medication affecting coagulation and patients with mixed symptoms (e.g. concomitant passive incontinence, constipation, and rectal evacuatory disorder).
	Interventions	PTNS using Uroplasty Urgent PC on either leg. Stimulation was gradually increased until sensation was perceived in the foot, or motor flexor response was seen at the great toe. Treatment involved 12 weekly sessions of 30 minutes duration, followed by 2 sessions at 2-week intervals, and one a month later. Outcome were assessed in March 2009 at a median follow-up of 9 months (range, 3–14) from the end of treatment.
	Outcomes	Bowel diaries recording weekly FI episodes, CCIS and degree of faecal urgency (recorded as patients perceived ability to defer defaecation) recorded prior to and after treatment.
Findlay *et al*. 2010	Methods	Study Design: Single centre non-randomised retrospective case series. Follow-up: Conducted at month 4 (i.e. one month after treatment cessation).
	Participants	Thirteen consecutive patients with FI. Age and sex of patients not detailed. Inclusion Critria: FI of at least 6 months' duration, failure of medical and non-invasive interventions (including pelvic floor physiotherapy and biofeedback). Exclusion criteria: Age under 18 years, coagulopathy, neuropathy, implanted pacemaker or cardiac defibrillator, and pregnancy or intention to become pregnant.
	Interventions	PTNS using Uroplasty Urgent PC using either leg. Successful placement confirmed by elicitation of digital plantar flexion or abduction. PTNS undertaken for 15 min at the highest current (0–9 mA) not causing a motor response, at frequency of 20 Hz. After 15 min, current was increased by 1 mA for a further 15 min. Weekly 30-min sessions for 12 consecutive weeks.
	Outcomes	Bowel diaries recording monthly episodes of FI to flatus, liquid and solid. Hospital Anxiety and Depression (HAD) Score, the International Consultation on Incontinence Questionnaire Anal Incontinence Symptoms and Quality of Life Module (ICIQ-B), and

		FIQOL, completed 4 weeks before and after treatment.
Hotouras *et al*. 2012	Methods	Study Design: Single centre non-randomised prospective case series. Follow-up: 3 months i.e. immediately following cessation of treatment.
	Participants	88 female patients. Mean age 58.0 +/- 13.6 years. Inclusion criteria: Female patients with FI over a 3-year period (2008-2011). Exclusion criteria: none listed.
	Interventions	PTNS using Uroplasty Urgent PC on either leg. Current gradually increased until sensation elicited in foot or motor flexor response seen in great toe. Twelve 30-minute treatment sessions once or twice weekly over a 6–12 week period. If treatment successful two further treatments 2 weeks apart and one a month later.
	Outcomes	Bowel diaries recording weekly episodes of faecal incontinence. CCIS score. All data were collected prior to treatment and immediately after the final treatment visit.
Arroyo *et al.* 2014	Methods	Study Design: Two centre non-randomised prospective case series. Follow-up: 6 months
	Participants	16 patients (15 female). Mean age 56.5 +/- 10.9 years. Inclusion criteria: Patients with faecal incontinence of a diverse cause, who were refractory to medical treatments. Patients were selected on the basis of a 90-180 degree sphincter lesion. Exclusion criteria: Inability to communicate (e.g. patients with Alzheimer's disease, among others), acute anatomical problems with possible surgical resolution (less than 3 months) and unwillingness to consent to participate in the study.
	Interventions	PTNS using Uroplasty Urgent PC. Leg not mentioned. Successful placement was confirmed by presence of electric sensation 5cm above and below the insertion site or by plantar flexion of toes. PTNS was undertaken at the highest setting which did not cause a motor response or pain. Twelve weekly 30-minute treatments were undertaken. If clinical improvement occurred, patients received an additional six sessions every 2 weeks.
	Outcomes	At 6 months: Median CCIS had decreased from 10 to 5 (p=0.006). Retention time had improved from <1min in 75% patients at baseline to only 2 patients (p=0.008)./ VAS increased from 6 to 7.5 (p>0.05). Maximum resting and squeeze pressures increased significantly.
Al Asari *et al.* 2014	Methods	Study Design: Single centre non-randomised prospective case series (PTNS and SNS patients over same time period) Follow-up: 1 year

	Participants	78 patients (71 female). PTNS: 21 (21 female) mean age 62.3 +/- 15.3. SNS 29 (32 female) mean age 60.1 +/-12. Inclusion criteria: Patients who had failed to respond to conservative treatment, including dietary modification, anti-diarrhoeal drugs and biofeedback therapy for 3-12 months. Exclusion criteria: Cardiac pacemaker, neurological disease, diabetes, psychiatric disease, coagulopathy, unable to attend repeated weekly sessions, local skin disease at site of puncture.
	Interventions	PTNS using Uroplasty Urgent PC. Leg not mentioned. Correct stimulation parameters were seen by plantar flexion of ipsilateral toes but without any sensation or contraction of the pelvis. Unilateral stimulation performed twice per week for 6 weeks then once per week for 3 weeks. Thereafter patients received one session every 15 days, followed by one every 3-4 weeks and then once every 5-6 weeks as required.
	Outcomes	Assessments at 6 weeks, 3 months, 6 months and 12 months. Primary outcome was statistically significant reduction in Wexner FI score at 6- and 12-month periods compared to baseline. Secondary outcomes included improvement in quality of life rated by FIQL questionnaire and treatment-related complications.
Hotouras *et al.* 2014	Methods	Study Design: Single centre non-randomised prospective case series of PTNS and SNS, including a sub-group analysis using a 1-1 'pseudo-case control model'. Follow-up: 3 months.
	Participants	146 patients (128 female). Median age 56 (range 15-83). Sub-group analysis included 37 SNS patients and 37 selected PTNS patients from above group. Inclusion: Not specified. Exclusion: Not specified.
	Interventions	PTNS delivered with Uroplasty Urgent PC, which was performed over 12 nurse-led outpatients sessions, according to the previously published departmental protocol.
	Outcomes	All patients had the following outcomes assessed at baseline and 3 months: CCIS score, ability to defer defaecation, number of weekly FI episodes. A 10 year treatment cost comparison was also documented.
De la Portilla *et al.* 2014	Methods	Study Design: Single centre non-randomised prospective case series. Follow-up: 3 months, 8 months, 14 months, 27 months.
	Participants	30 patients (21 female). Median age 56 +/- 11.2 years. Inclusion: Age 18-80, severe FI with CCIS at least 10, more than four FI episodes per 28 days, duration of FI longer than 6 months, failure of conservative treatments (fibre plus loperamide, biofeedback or bulking agents and integrity of the external anal

		sphincter. Exclusion: severe cardiopulmonary disease, severe venous insufficiency of lower limbs, cardiac pacemaker or implantable defibrillator, inflammatory bowel disease, irritable bowel syndrome, uncontrolled diabetes with peripheral neuropathy, immunosuppression, anal fissure, anal fistula or abscess, pregnancy.
	Interventions	PTNS delivered with Uroplasty Urgent PC unilaterally. Amplitude was slowly increased until plantar flexion of the large toe or fanning of the other toes occurred. The intensity of stimulation was set at a well-tolerated level. Patients underwent 12 weekly outpatient treatment sessions, each lasting 30 minutes (first phase). Further treatment was given to patients who achieved a 40% or more decrease in CCIS. This consisted of treatments every other week for 2 months followed by every 3 weeks for 2 months and finally one session in 1 month.
	Outcomes	Outcomes were measured before treatment, immediately after 3 months treatment, after 8 months, after 14 months and after 27 months. Outcomes included CCIS, FIQL and a VAS for overall quality of life. Anorectal manometry was performed pre treatment and after 8 months treatment.
Hotouras *et al.* 2014	Methods	Study Design: Single centre non-randomised prospective case series. Follow-up: 3 months, median 29 months (range 15-45 months).
	Participants	115 patients (103 female). Median age 56 (range 30-83 years). Inclusion: Not specified Exclusion: Not specified
	Interventions	PTNS delivered with Uroplasty Urgent PC according to published departmental protocol. Treatments generally delivered as 12 half-hour treatments over a period of 3 months, followed by 3 'weaning' sessions and then 6-monthly maintenance 'top-up' sessions.
	Outcomes	CCIS, bowel diaries, deferment time and FIQoL scores all obtained pre-treatment, at 3 months and at final follow-up.
Lopez Delgado *et al.* 2014	Methods	Study Design: Single centre non-randomised prospective case series. Follow-up: 3 months and 6 months
	Participants	24 patients (19 female). Mean age 62.1 +/- 10.1 years. Inclusion: Patients with FI due to various causes who were refractory to medical and surgical treatment. Exclusion criteria: Inability to communicate, dementia, acute trauma for which surgery was possible and refusal to enter the study.

	Interventions	PTNS using Uroplasty Urgent PC. No mention of leg. Successful placement was confirmed by presence of electric sensation 5cm above and below the insertion site or by plantar flexion of toes. PTNS was undertaken at the highest setting which did not cause a motor response or pain. Twelve weekly 30-minute treatments were undertaken. If clinical or anal manometric improvement occurred, patients received an additional six sessions every 2 weeks.
	Outcomes	CCIS. Time to deferment of defaecation. Fecal Incontinence Quality of Life score. Incontinence diary dividing patients into groups: <3 weekly faecal incontinence episodes (mild), 3-7 weekly faecal incontinence episodes (moderate) and >7 weekly faecal incontinence episodes (severe). Perception of the degree of incontinence using a visual analogue scale (0 worst to 10 best).

Table 43: Other outcomes in trials of transcutaneous tibial nerve stimulation

Reference	Outcome	Results
Queralto *et al*.	Anorectal manometry	No change from baseline to post-treatment
Vitton *et al*.	VAS for symptoms	42% reported symptomatic improvement at 3 months
	VAS for QoL	Improved by 50% in same 42% of patients as above
	Time to defer defaecation	Improvement reported in 25% of patients
Vitton *et al*.	VAS symptom improvement	54% reported symptomatic improvement at 3 months
	GIQOL	Not predictive of treatment success. No other data presented
Eleouet *et al*.	VAS for subjective improvement	Mean VAS: 63% perceived improvement at 1 month with mean improvement of 25% (±30%)
	FIQL score	Mean FIQL improved significantly in all areas at 3 months but only coping/behaviour and general at 6 months
	KESS score	Mean KESS score improved significantly at 3 months but not at 6 months
	ADS score	Mean ADS anxiety score improved significantly at 3 months but not at 6 months
Leroi *et al*.	FIQL score	Marked improvement in all four domains
	Anorectal manometry	Significant improvement in maximum squeeze pressure after 3 months treatment (but not resting pressure, squeeze duration or rectal sensitivity)
George *et al*.	St Mark's Continence Score	Improvement in incontinence score from mean(s.d.) 18.5(3.1) to 14.7(6.7) after 3 months; reduction in bowel movements from 2.6(1.4) to 2.4(1.3) per 24 h; increase in deferment to defaecation time from 1.9(0.9) to 2.2(2.4) min (no statistical analysis reported)
	FIQL score	
	SF-36® QoL score	Improvements in all domains of SF-36® (no statistical analysis reported)
	Anorectal manometry	Improvement in peak squeeze pressure after 3 months treatment (but not resting pressure, rectal or anal sensitivity)
Thomas *et al.*	Bowel diaries	Percentage reduction in frequency of incontinent episodes: Median of 60% in the daily group and median of 50% in the twice-weekly group. Weekly frequency of defaecation: No significant changes in either group. Ability to defer defaecation: No significant change in either group.
	St Mark's Continence Score	Twice weekly group showed significant improvement from 21 (4) to 17 (7) (p=0.012). No significant reduction was seen in the daily group 18 (5.25) to 18 (4.50) (p=0.07).
	VAS for bowel satisfaction	Improved significantly in both groups. Daily group: 10 (21) to 30 (23.25) (p=0.01). Twice-weekly group: 10 (39) to 30 (40) (p=0.004).
	FIQL	No significant improvement in any domain in the twice-weekly group. Significant improvement in the daily group in the lifestyle and embarrassment domains only.
	SF-36	No improvement in any domain in the twice-weekly group. Improvement in the physical functioning domain only in the daily group.
	Effect of body mass index and ankle circumference	Neither had any effect upon the change in incontinent episodes.

Thomas *et al.*	Bowel diaries	Median percentage reduction in FI episodes for the group was 66%. Ability to defer defaecation was significantly improved from median (SD) of 3 (4) minutes to 5 (8) minutes (p=0.03). Patients who experienced a reduction in FI episodes returned to baseline in a median (SD) of 3 (1) weeks.
	VAS for bowel satisfaction	Improved significantly from median 10 (25) to 20 (52.5) (p=0.02).
	FIQL	Significant improvement in lifestyle domain from median (IQR) 2.1 (0.6) to 2.5 (1.6) (p=0.01).
	SF-36	Significant improvement in the general health domain from median (IQR) 41.5 (15.7) to 46.2 (14.9) (p=0.04).
	Effect of body mass index and ankle circumference	No effect of body mass index or ankle circumference on change in incontinent episodes.

VAS, visual analogue scale; QoL, quality of life; GIQOL, Gastrointestinal Quality of Life Index; FIQL, Faecal Incontinence Quality of Life Scale; KESS, ADS**,** Anxiety and Depression Scale*;* SF-36®, Short Form 36 (QualityMetric, Lincoln, Rhode Island, USA); IQR, Interquartile Range.

Table 44: Characteristics of TTNS studies (by publication date)

Study	Characteristic	Description
Qualtero *et al.* 2006	Methods	Study Design: Single-centre prospective case-series. Follow-up: 1 month and 4 months after treatment cessation. Total study duration: 4 months.
	Participants	10 female patients referred for idiopathic anal incontinence. Inclusion criteria: No sonographic sphincter defect, no anatomical rectal prolapse, and clinical failure of medical treatments and biofeedback rehabilitation or trans sacral neuromodulation. Exclusion criteria: None listed.
	Interventions	TENS provided via a Cefar Primo stimulating TENS unit. Negative electrode placed on ankle skin behind internal malleolus and positive electrode 10cm above this. Adequate position of electrode determined by visualisation of rhythmic flexion of toes during stimulation. Intensity level selected as that immediately under the threshold of motor contraction. Applied daily for 4 weeks at the patient's home. Outcomes assessed after 4 weeks, and patients discontinued treatment in case of failure, or continued for 2 months, 5 days per week, if benefit was observed.
	Outcomes	CCIS score at baseline compared to after 4-weeks treatment and at 4 months for those who continued treatment. Anal manometry before compared to after 4-weeks treatment.
Vitton *et al.* 2009	Methods	Study Design: Single-centre prospective case-series. Follow-up: 3 months i.e. immediately after treatment cessation. Total study duration: 3 months.
	Participants	12 (F=9) with inflammatory bowel disease and FI. Median age 51 years (range 29-64). Inclusion criteria: Age >18 years, IBD stable for 3 months with no treatment modification, FI symptoms for >6 months (involuntary passage of stool and CCIS score>5/20). Exclusion criteria: Pregnancy, active IBD (Harvey-Bradshaw index >8), pouchitis or anastomotic stenosis in case of ileoanal anastomosis, uncontrolled diabetes, neurological diseases or spinal cord lesion.
	Interventions	TENS provided using a TENStem Eco stimulating TENS unit. Negative electrode placed on the ankle skin behind internal malleolus and positive electrode 10cm above this. Intensity level

		set just below intensity inducing a sensitive perception from the patient. Treatment applied by the patient for 20 minutes every day for 3 months at the patients home.
	Outcomes	CCIS score and Harvey-Bradshaw Index questionnaires at baseline and following 3 months of treatment. Analogue scales for symptoms and quality of life collected following 3 months treatment.
Vitton *et al.* 2010	Methods	Study Design: Single-centre prospective case-series. Follow-up: 3 months i.e. immediately after treatment cessation. Those experiencing treatment success continued treatment and were followed up after a mean period of 15 months (range 9-35 months). Total study duration: 35 months.
	Participants	24 (F=22) consecutive patients referred to the department due to FI. Inclusion criteria: Age >18 years, FI symptoms for >6 months, previous failure of medical treatment and/or biofeedback therapy. Exclusion criteria: Pregnancy, severe distal venous insufficiency, severe cutaneous local lesion, active anal lesion, inflammatory bowel disease, use of a cardiac pacemaker or implantable cardiac defibrillator.
	Interventions	TENS provided using a TENStem Eco stimulating TENS unit. Negative electrode placed on ankle skin behind internal malleolus and positive electrode 10cm above this. Intensity level set just below the intensity inducing a sensitive perception from patient. Stimulation parameters 200 μs, 10-Hz and 10-30mA, and treatment applied by patient for 20 minutes every day for 3 months at patient's home. For those patients experiencing improvement in symptoms, treatment continued with same parameters though duration not noted.
	Outcomes	CCIS score and GIQOL Index at baseline, following 3 months treatment and at final follow up for those continuing therapy. Analogue scales for symptom improvement collected at 3 months and final follow-up.
Eleouet *et al.* 2010	Methods	Study Design: Single-centre prospective case-series. Follow-up: 1 month i.e. immediately after treatment cessation. Those experiencing treatment success continued treatment and were followed up again at 3 months, after which those with no benefit stopped treatment, and the remainder were followed up at 6 months. Total Study Duration: 6 months.
	Participants	32 (F=30) consecutive patients referred to the department due to FI. Age 61 +/-13 years. Inclusion criteria: Severe incontinence to faeces with CCIS from 11-20, failure of previous conservative therapy (i.e. biofeedback, diet

		modification laxatives or anti-diarrhoeal drugs). Exclusion criteria: Soiling as a unique symptom (i.e. without any flatus incontinence), overt rectal prolapse, faecal impaction, total proctectomy, local inflammation, inflammatory bowel disease and insulin-dependent diabetes.
	Interventions	TENS provided using a TENStem Eco Program P3 stimulating TENS unit. Negative electrode placed on the ankle skin behind internal malleolus and positive electrode 10cm above this. Correct position of negative electrode determined by visualisation of rhythmic flexion of the toes. Intensity level set just below threshold determining motor contraction. Stimulation frequency applied at 10Hz and pulse width of 200 μs in continuous mode. Patients asked to apply treatment at least 20 minutes twice daily in their own home. For those patients experiencing improvement in symptoms after 1 month of treatment, treatment was continued.
	Outcomes	Level of subjective improvement for each patient following 1 month of treatment was the main endpoint with a 10cm visual analogue scale. CCIS score and FIQL Index KESS score and anxiety and depression scale (ADS) were performed at baseline, following 1 month of treatment and 3 and 6 months for those who continued therapy.
Thomas *et al*. 2013	Methods	Study Design: Single-centre prospective case-series. Follow-up: 6 weeks (1.5 months) i.e. immediately after treatment cessation.
	Participants	17 (15 females) patients consecutively recruited (20 originally however 3 excluded from analysis due to pregnancy (n=1) and unknown (n=2). Age median (IQR) 61 (24.5). Inclusion criteria: Age 18-80 years, FI defined as at least 2 episodes per week of involuntary loss of either liquid or solid stool as defined by a baseline bowel diary, completed biofeedback and conservative therapy, no previous neuromodulation. Exclusion criteria: Spinal pathology, recent surgery, peripheral vascular disease, previous anorectal surgery within the past year, external rectal prolapse, active inflammatory bowel disease, pregnancy, inability to apply the device independently.
	Interventions	All patients performed treatments at home following one to one instruction on the use of TTNS, written instructions and a photograph demonstrating the electrode pad and lead position. TTNS was performed on both ankles simultaneously for 30-minutes daily, for a 6-week period. TTNS given using NeuroTrac Continence device (Verity Medical Ltd, United Kingtom) via two 50mm x 50mm electrode pads. The live pad was placed posterior and superior to the medial malleolus and the ground pad was placed 10cm cephalad to this. Continuous stimulation at pulse width 200 microseconds and frequency 10Hz was used. Amplitude

		was set to produce a sensory stimulus in the ipsilateral foot, at a tolerable intensity.
	Outcomes	Outcomes were measured at baseline and immediately following the 6-week course of treatment. These included two 2-week bowel diaries, which recorded frequency of FI episodes, frequency of defaecation time and the deferral time to defaecation; a visual analogue scale asking patients 'how happy are you with the way your bowels have been functioning' (range 0, very unhappy to 100, very happy); Faecal Incontinence Quality of Life Score (FIQL); SMCS (St Mark's Continence Score) and SF-36. The body mass index and ankle circumference were also measured.

9.5 Appendix 5: CONFIDeNT subgroup analyses

Results of sub-groups analysis on primary outcome (N = 227)

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

Notes:

OR (odds ratio) corresponds to the adjusted odds ratio for PTNS vs. sham from a logistic mixed effects model, adjusted for baseline mean FI episodes per week, sex and includes a random effect for study centre.

Missing data were multiply imputed using multilevel multiple imputation to create 10 complete datasets for analysis, the results of which were combined using Rubin's rules.

9.6 Appendix 6: CONFIDeNT sensitivity analyses

Results of sensitivity analysis 1(excludes 16 patients with no FI episodes in baseline bowel diary)

Outcome	Type	N	Estimate	Lower CI	Upper CI	P-value	Model based ICC
>= 50% reduction in FIE	OR	211	1.325	0.736	2.385	0.348	<0.001
>= 25% reduction in FIE	OR	211	1.314	0.747	2.311	0.344	<0.001
>= 75% reduction in FIE	OR	211	1.643	0.775	3.484	0.195	0.212
100% reduction in FIE	OR	211	1.670	0.596	4.674	0.330	0.008
Change in FIE	beta	211	-2.468	-4.533	-0.403	0.019	<0.001
Change in urge FIE	beta	211	-1.557	-2.881	-0.232	0.021	<0.001
Change in passive FIE	beta	211	-0.736	-1.850	0.378	0.195	0.1
FI QoL embarrassment	beta	211	0.049	-0.149	0.247	0.630	<0.001
FI QoL coping	beta	211	0.021	-0.172	0.214	0.831	0.116
FI QoL lifestyle	beta	211	0.105	-0.070	0.280	0.236	<0.001
FI QoL depression	beta	211	0.025	-0.294	0.344	0.873	<0.001
SF36 physical functioning	beta	211	-2.025	-7.515	3.464	0.469	<0.001
SF36 role-physical	beta	211	1.646	-8.860	12.152	0.758	n/a
SF36 bodily pain	beta	211	-1.039	-7.114	5.036	0.737	<0.001
SF36 general health	beta	211	0.159	-4.759	5.076	0.949	<0.001
SF36 vitality	beta	211	-2.930	-8.194	2.334	0.273	n/a
SF36 social functioning	beta	211	6.343	0.010	12.676	0.051	0.017
SF36 role emotional	beta	211	-5.461	-15.881	4.959	0.302	n/a
SF36 mental health	beta	211	0.031	-4.477	4.540	0.989	0.065
St. Mark's continence score	beta	211	-0.139	-1.163	0.885	0.790	<0.001
Patient centred outcomes	beta	211	-0.562	-1.123	-0.001	0.050	<0.001
EQ-5D index score	beta	211	-0.017	-0.081	0.048	0.610	0.019
GI QoL	beta	211	-1.558	-5.566	2.449	0.442	n/a
Likert scale of success	beta	211	0.786	-0.123	1.694	0.091	0.009

OR (odds ratio) corresponds to the adjusted odds ratio for PTNS vs. sham from a logistic mixed effects model, adjusted for baseline mean FI episodes per week, sex and includes a random effect for study centre. beta corresponds to the adjusted difference in means for PTNS vs. sham from a linear mixed effects model, adjusted for baseline level of outcome (except Likert scale of success), sex and includes a random effect for study centre. n/a indicates that the unconditional ICC (intracluster coefficient) was < 0 and the corresponding outcomes were modelled using linear regression without an adjustment for study centre. Missing data were multiply imputed using multilevel multiple imputation to create 10 complete datasets for analysis, the results of which were combined using Rubin's rules.

Results of sensitivity analysis 2: excluding centres that recruited <5 patients (2 centres, 4 patients).

Outcome	Type	N	Estimate	Lower CI	Upper CI	P-value	Model based ICC
>= 50% reduction in FIE	OR	223	1.234	0.693	2.196	0.476	<0.001
>= 25% reduction in FIE	OR	223	1.220	0.698	2.132	0.485	<0.001
>= 75% reduction in FIE	OR	223	1.634	0.776	3.438	0.196	0.214
100% reduction in FIE	OR	223	1.690	0.609	4.693	0.315	0.006
Change in FIE	beta	223	-2.158	-4.034	-0.283	0.024	<0.001
Change in urge FIE	beta	223	-1.501	-2.752	-0.25	0.019	<0.001
Change in passive FIE	beta	223	-0.592	-1.637	0.453	0.267	0.094
FI QoL embarrassment	beta	223	0.020	-0.166	0.206	0.83	<0.001
FI QoL coping	beta	223	0.017	-0.168	0.203	0.855	0.1
FI QoL lifestyle	beta	223	0.092	-0.072	0.257	0.27	<0.001
FI QoL depression	beta	223	0.010	-0.301	0.321	0.945	<0.001
SF36 physical functioning	beta	223	-1.479	-6.674	3.717	0.576	<0.001
SF36 role-physical	beta	223	1.462	-8.684	11.608	0.777	n/a
SF36 bodily pain	beta	223	-0.844	-6.712	5.024	0.778	<0.001
SF36 general health	beta	223	-0.021	-4.676	4.634	0.993	<0.001
SF36 vitality	beta	223	-3.857	-8.875	1.161	0.131	n/a
SF36 social functioning	beta	223	5.419	-0.585	11.423	0.078	0.012
SF36 role emotional	beta	223	-5.297	15.405	4.811	0.303	n/a
SF36 mental health	beta	223	-0.877	-5.237	3.483	0.693	0.031
St. Mark's continence score	beta	223	0.052	-0.928	1.032	0.917	<0.001
Patient centred outcomes	beta	223	-0.575	-1.121	-0.029	0.039	<0.001
EQ-5D index score	beta	223	-0.020	-0.082	0.042	0.524	0.017
GI QoL	beta	223	-1.269	-5.182	2.643	0.521	n/a
Likert scale of success	beta	223	0.856	-0.016	1.728	0.055	0.02

OR (odds ratio) corresponds to the adjusted odds ratio for PTNS vs. sham from a logistic mixed effects model, adjusted for baseline mean FI episodes per week, sex and includes a random effect for study centre.

beta corresponds to the adjusted difference in means for PTNS vs. sham from a linear mixed effects model, adjusted for baseline level of outcome (except Likert scale of success), sex and includes a random effect for study centre.

n/a indicates that the unconditional ICC (intracluster coefficient) was < 0 and the corresponding outcomes were modelled using linear regression without an adjustment for study centre.