MONASH University

Identification of co-existing conditions in functional gastrointestinal-disorders, and novel strategies in the prevention and management of functional gastrointestinal disorders

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ABSTRACT

Current practices in identifying and managing functional gastrointestinal disorders (FGID) are not optimal and appear to centre on the involvement of the gastroenterologist. Based on the overall hypothesis that a nurse-specialist can and should play increasing roles in such practice, the current thesis aimed to address specific aspects of the nurse's role in diagnostic, therapeutic and preventive strategies.

A role in the diagnostic pathway was investigated by performing a retrospective audit of data from a protocol-driven nurse-led service of women referred for suspected IBS in New Zealand. A proportion of patients (19%) did not meet Rome III criteria for IBS of whom two thirds had another FGID. Of those who did, the use of red flags and simple investigations defined 13% who had an alternate diagnosis that required different management. Clinical risk factors of pelvic issues that might require alternative approaches - endometriosis and rectocele, both common (31% respectively) in this cohort – were also defined. Therapeutically, nurse-led education of patients with IBS in a low FODMAP diet was successful and identified that those with endometriosis were significantly more likely to respond than those without (72% vs 49%).

Constipation in hospitalised patients is a poorly studied area and management is usually reactive after its development. A nurse-led structured care-plan for prevention, early detection and pro-active management in an acute brain-injury unit was developed. Its

implementation achieved greater confidence by nurses in management of this common complication. Improved patient outcome was implied, but requires formal study.

A novel, nurse-led non-pharmacological strategy for dealing with symptoms of constipation and gastroparesis – trans-abdominal interferential electrical stimulation – was investigated, initially by an observational case series in which gratifying benefits were reported. A randomised controlled trial using 6 weeks of IFT or a novel sham therapy was subsequently conducted in women with constipation where active therapy was associated with significant improvement in several relevant clinical outcomes. This included the primary outcome, where 60% of participants in the IFT treatment group achieved more than two spontaneous bowel movements a week, compared to 13% of those with sham treatment (P=0.02). Of importance, the therapy was readily accepted by patients and no treatment-related adverse effects were observed. In a pilot study, no objective physiological measures (anorectal manometry or colonic transit time) were consistently altered by therapy or associated with response.

In conclusion, the spectrum of nurse-led diagnostic, preventive and therapeutic actions studied provided much-needed evidence for potentially key roles of the nurse in managing patients with FGID. Use of protocols ensure safety whether at the advanced practice level or for nurses with different levels of experience in the ward setting. Efficacy of nurse-led IFT in treating patients with gastrointestinal dysmotility provides further evidence of the impact that nurses can have in management algorithms for patients with FGID. New clinical models

of care need to be designed and evaluated in an attempt to improve the experience and outcome of patients with such conditions.

DECLARATION

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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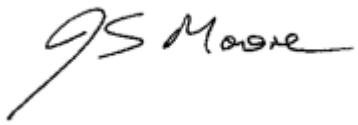

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PUBLICATIONS

The following papers have been published during my PhD tenure (2014-2018) and relate to findings and concepts discussed in this thesis.

Moore, J.S., Gibson, P.R., Perry, R.E. & Burgell, R.E. (2017) Endometriosis in patients with irritable bowel syndrome: Specific symptomatic and demographic profile, and response to the low FODMAP diet. *Aust N Z J Obstet Gynaecol 2017 1-5* DOI:10.1111/ajo.12594

Moore, J.S., Gibson, P.R., Perry, R.E. & Burgell, R.E. (2016) Use of additional red flags and simple investigations improves identification of alternative therapeutic targets in patients presenting with irritable bowel syndrome. *Accepted for publication Oct 2016 Gastroenterology Nursing*

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Thank you. Jess Wood, who is overseeing the new model of care for the functional gut service; you are an amazing organiser, and you make this new project tick. I am very glad to have someone so organised leading the way.

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X

ABBREVIATIONS

3-D HDAM	3D High Definition Anorectal Manometry
5-HT	5 – hydroxytryptamine
ABIU	Acquired Brain Injury Unit
BM	Bowel Motion
BNO	Bowels Not Open
BSL	Blood Sugar Level
BSS	Bristol Stool Scale
CCCS	Cleveland Clinical Constipation Score
CNS	Clinical Nurse Specialist
CRH	Corticotropin Releasing Hormone
DBE	Diaphragmatic Breathing Exercises
DDV	Defaecatory Desire Volume
DM	Diabetes Mellitus
EAS	External Anal Sphincter
ENS	Enteric Nervous System
EPS	Epigastric Pain Syndrome
FCS	First Constant Sensation
FGID	Functional Gastrointestinal Disorders
FODMAP	Fermentable Oligosaccharides Disaccharides Monosaccharides And Polyols
GABA	Gamma-aminobutyric acid

GCSI	Gastroparesis Cardinal Symptom Index
GDH	Gut Directed Hypnotherapy
GI	Gastrointestinal
GIQLI	Gastrointestinal Quality of Life Index
GORD	Gastro-Oesophageal Reflux Disorder
HRAM	High Resolution Anorectal Manometry
IAS	Internal Anal Sphincter
IBS	Irritable Bowel Syndrome
IBS-C	Irritable Bowel Syndrome –Constipation predominant
IBS-GAI	Irritable Bowel Syndrome Global Assessment of Improvement
ICU	Intensive Care Unit
ICC	Interstitial Cells of Cajal
IFT	Interferential Therapy
IQR	Interquartile Range
ITT	Intention to Treat
Ix	Investigations
JEJ	Jejeuno feeding tube
KESS	Knowles Eccersley Scott Score
LIF	Left Iliac Fossa
MRI	Magnetic Resonance Imaging
MTV	Maximum Tolerated Volume
NGT	Naso-gastric Tube
PAC-QOL	Patient Assessment Constipation Quality of Life

PAC-SYM	Patient Assessment Constipation Symptoms
PDS	Post-prandial Distress Syndrome
PEDs QOL	Paediatric Quality of Life
PEG	Percutaneous Endoscopic Gastrostomy
PEG	Polyethyleneglycol
PP	Per Protocol
PRN	Pro Re Nata – as needed
PTNS	Percutaneous Tibial Nerve Stimulation
QOL	Quality of Life
RAIR	Recto-anal Inhibitory Reflex
RCT	Randomised Controlled Trial
RF	Red Flags
RMO	Resident Medical Officer
SF-12	Short Form 12 (questionnaire)
SNS	Sacral Nerve Stimulation
TPN	Total Parenteral Nutrition
VAS	Visual Analogue Scale

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CHAPTER 1: - INTRODUCTION

1.1 Anatomy and physiology of the gastrointestinal tract pertaining to this thesis

The bowel, in its most simplistic form, is a long, cylindrical transporter of substrates from the mouth to the anus, which allows absorption of nutrients, electrolytes and fluids before waste products are expelled. Of course, in reality its functions are much more complex.

The bowel is divided, based on embryology, into 3 sections; the foregut, which forms the oesophagus, stomach, proximal duodenum, liver and biliary system and pancreas[1]. This is followed by the midgut, which forms the distal duodenum, jejunum, ileum, caecum, appendix and colon from the ascending colon to the mid transverse colon. The 3rd section comprises the hindgut, which forms the colon from mid transverse to sigmoid and rectum.

Given the complexity of the gastrointestinal tract, for the purpose of this thesis, the focus will be only on gastric and colonic function, 2 areas of the bowel understood to be significantly impacted by motility disturbances.

1.1.1. Neuronal control of the gastrointestinal tract

The gastrointestinal (GI) tract is controlled by a complex interaction between the extrinsic nervous system (also called the autonomic nervous system) and the intrinsic gastrointestinal nervous system (also called the enteric nervous system)[2]. The efferent component of the extrinsic nervous system is comprised of the sympathetic and parasympathetic nervous system and links the gut to the central

nervous system (CNS), creating in conjunction with the afferent component, the bi-directional gut-brain axis[2]. This axis also has bidirectional soluble factors that travel via the circulation. A key mediator of stress responses in the gut-brain axis is the hormone, corticotropin-releasing hormone (CRH), which affects motility, sensory perception in the gut and mood[3]. A number of other neurotransmitters also are involved with both the enteric and extrinsic nerves; for instance, serotonin (5-hydroxytryptamine, 5-HT) and other peptides released by the enterochromaffin cells that exert effects on motility, secretion and modulate sensory transmission between the CNS and the gut[4].

1.1.1.1 The enteric nervous system

The enteric nervous system (ENS) is a complex neuronal system comprising of intrinsic motor and sensory neurons, and interneurons, with their cell bodies contained within the wall of the gut and glial cells. The ENS has multiple regulatory functions including the coordination of secretion, motility, defense mechanisms and digestion within the gut[5, 6]. This system is unique in that it can function independently without contact with the CNS. However, the CNS is still in close communication, via the extrinsic nervous system, the main lines of neural communication being via the vagal and spinal nerves, including metabolic, immune and endocrine mediators[7].

1.1.1.1.1. The enteric nervous system within the stomach

The ENS in the stomach is, like the rest of the GI tract, able to function autonomously[8], but generally works in conjunction with the autonomic nervous system and the CNS. Most of the contractile, motor activity is triggered by the interstitial cells of Cajal (ICC), the pacemaker cells contained within the antrum of the stomach[6, 9]. Stomach activity is less dependent on the ENS and is predominantly driven by ICC function as opposed to the small intestine and colon[6]. In the stomach the ICC are directly linked to smooth muscle cells where a coordinated electrical activity pattern creates a rhythm for gastric motility[9].

1.1.1.1.2. The enteric nervous system in the colon

The various regulatory functions of the colon are coordinated by the ENS[6, 10]. Both sensory and motor neurons are found within the myenteric plexus and the submucosal plexus, though motor function is more predominant. Sensory neurons and endocrine cells respond to the variety of stimuli provided by contents of the gut, driving much of the reflex circuits[11]. While extrinsic pathways have a modulatory effect on the motor function, much of the control is directly via the enteric motor neurons. The ENS contains sensory, excitatory, inhibitory and secretory motor neurons and interneurons. This creates the patterns of motility and secretion across large distances within the bowel. The ENS also contains intrinsic primary afferent neurons, which are activated via stretch, mechanical or chemical stimuli, and play a nociceptive role[6]. Nociception is important in both the small and large intestine where detection of harmful substances leads to secretion of copious quantities of fluid and contractions. This results in vomiting initiated by retropulsive reflexes in the proximal small intestine, and/or diarrhoea from the large bowel[6].

1.1.1.2 The extrinsic nervous system

1.1.1.2.1 The extrinsic nervous system within the stomach

Motor function within the stomach is modulated by the sympathetic and parasympathetic nerves. The latter arises from the vagal nerve [9] and acts via vagovagal reflexes, where the vagal cell bodies directly transmit information to the vagal motor neurons[8]. The sympathetic nerves arise from T6-T9 in the spine where they inhibit the release of acetylcholine in the myenteric plexus, thereby inhibiting gastric function[8].

1.1.1.2.2 The extrinsic nervous system and the colon

Colorectal function is modulated by extrinsic innervation via the descending autonomic pathways. Sensory innervation of the proximal colon is via afferent fibres running parallel to the vagus nerve[11]. Pelvic afferent fibres innervate the distal colon and are involved in colorectal sensation[12]. Physiological and visceral sensations such as the desire to defaecate, are transmitted along the pelvic afferents to converge on the spinal neurons[11]. These fibres run parallel to the sacral parasympathetic and sympathetic pathways. Efferent supply is via sympathetic and parasympathetic innervation, which modulates both sensory and motor functions, the parasympathetic innervation originating from the vagus nerve for the proximal gut and from S2-S4 nerve roots for the hindgut[10]. Sympathetic impulses arise from T9-L2. The parasympathetic nerves stimulate gut activity in both motility and secretory functions whereas the sympathetic system has an inhibitory function. The reverse occurs in the anal sphincter.

1.1.2 Anatomy, physiology and function of the stomach

In its simplest form, the GI tract is a tube comprised of smooth and/or striated muscle, and the submucosal and mucosal layers with different functions including digestion of foods and expulsion of waste[13]. Anatomically, there are several different functional regions in the stomach - the fundus, the antrum, the cardia, lesser and greater curvatures of the stomach and the pylorus[9]. The proximal stomach, or fundus, relaxes to accommodate food on arrival and this prompts a number of coordinated sequences[14]. These events are controlled by the gastric pacemaker, the ICC, which trigger waves of contraction within the stomach in order to propel food contents through into the small intestine[14, 15]. These waves begin at the greater curvature of the stomach and occur approximately 3 cycles per minute[9]. The presence of solid food triggers a peristaltic grinding response and secretion of digestive fluids.[16] The pylorus is able to distinguish between liquid and solid foods, thus allowing released of gastric contents in a precise, timely manner into the small intestine at a rate that facilitates

optimal absorption of nutrients. Foodstuff then traverse the small intestine in which digestion and subsequent absorption of nutrients, electrolytes and fluids occurs via a complex system that is outside the scope of this thesis.

1.1.3 Anatomy, physiology and function of the colon and anorectum

The large bowel has 6 anatomical regions that commence with the caecum, and progress distally to the ascending, transverse and descending colon, and the sigmoid colon, terminating with the rectum. The colon functions as more than just a transporter of waste. The proximal colon is critical for the absorption of water (up to 90% of the water that enters it) and salts as well as mixing of contents[17, 18]. It is also important for digestion that includes fermentation of complex carbohydrates and protein by anaerobic bacteria with subsequent delivery of nutrients (such as butyrate) to the colonic mucosa. The colon regulates the luminal environment via the secretion of hormones, mucus and fluids. The hindgut – distal transverse and left colon, is also a conduit for waste and a storage reservoir, with the rectum and anal canal important in maintaining continence and in the control of defaecation.

The colonic wall is comprised of muscle layers made up of both longitudinal and circular smooth muscle layers,[19] and the mucosa which comprises 3 layers - the muscularis mucosae, the lamina propria and the epithelium. Epithelial cells are of different types and include pluripotent stem cells, absorptive cells, mucus-secreting goblet cells and enteroendocrine cells, which release gut peptide hormones including serotonin[5, 18]. The roles of the mucosa are varied, and involve defence, absorption, regulation of appetite and neuro-endocrine signalling, as well as the interaction between the luminal environment, especially the microbiota and its products, and the gut[5].

The anorectum, an extension of the muscle and mucosal layers of the colon, has 2 components - the upper rectum originating from the hindgut in the embryonic stages, and the lower part of the

anorectum, formed from the cloaca, with the proximal anal canal surrounded by the levator ani muscles, a major component of the pelvic floor. A part of these, the pubo-rectalis muscle, maintains an acute ano-rectal angle needed for continence[18]. Surrounding the distal anal canal are the internal anal sphincter (IAS), which is smooth muscle formed by the continuation of the rectal muscle layer, and the external anal sphincter (EAS) comprised of skeletal muscle that is under voluntary control. Mechanoreceptors sense distension from stool in the rectum where a number of chemical and mechanical intrinsic responses occur to trigger relaxation of the internal anal sphincter (IAS)[5]. A combination of this with the extrinsic efferent component involved in the EAS allows control of defaecation.

1.1.4 Normal colonic and anorectal motility

1.1.4.1 Colonic motility

To function efficiently, the colon must propel its contents in an aboral direction. This is achieved by peristalsis, the rhythmic and co-ordinated contraction of the colonic smooth muscle that results in both movement and mixing of the luminal contents[18]. Transit of contents around the colon is via a range of contractions, from short duration contractions (called phasic contractions) to long sustained contractions resulting in changes of intestinal tone (tonic contractions). Phasic contractions are triggered by spikes in slow-wave activity, the frequency of which varies in different parts of the gastrointestinal tract[16]. Tonic contractions, in contrast, occur in response to stimuli, mechanical and neurogenic, and assist the efficacy of a phasic contraction. For example, an increase in gut-wall tone results in an overall decrease in the diameter of the gut lumen resulting in a more pronounced effect of phasic contractions. The ability of the gut to respond to intraluminal distension is known as compliance, where stretch and tension determine intraluminal pressure[16]. There is a circadian rhythm to such bowel activity where motility is inhibited during sleep, and triggered upon waking and post-prandially[18]. The colon responds to food and waking by emptying the ascending colon and filling the

recto-sigmoid region[20]. However, in health, there is much variability as to what determines "normal" when it comes to bowel function[18]. Although patterns of motility and rest are considered highly unpredictable, within a specific individual they generally remain predictable[17].

1.1.4.2 .Normal defaecation

Motility of the colon follows an organised pattern where an asymptomatic phase of increased propagated activity, or peristalsis, moving distally precedes defaecation by about an hour, followed by a symptomatic phase about three quarters of an hour later[18]. Coordination of the appropriate expulsion forces coupled with relaxation of the puborectalis muscle and sphincter complex are required for normal defaecation[17]. The sphincter complex consists of the IAS which is under involuntary parasympathetic control, and the EAS, which is comprised of skeletal muscle and is under voluntary control. Both sphincters play a role in maintaining continence as well as in defaecation[21].

As stool moves into the rectum, an increase in rectal volume induces an involuntary relaxation of the IAS. However, continence is maintained by the EAS in a voluntary manner. The increase in rectal volume also induces a sensori-motor response where there is the desire to defaecate[22]. At a socially acceptable time (toileting), the anorectal angle opens (via relaxation of puborectalis) and the start of a propulsive contraction causes both sphincters to relax. An appropriate increase in diaphragmatic intra-abdominal pressure contributes to relaxation of the EAS, and hip flexion further assists opening of the anorectal angle. After defaecation, the pelvic floor and EAS contract (the closing reflex) and any stool not passed is pushed back into the rectum.[18]

1.2 Functional gastrointestinal disorders - overview

The name functional gastrointestinal disorders (FGID) historically incorporate a broad group of conditions affecting the GI tract, which cause significant symptoms in the absence of identifiable

organic disease. It is now appreciated that distinct alterations and/or abnormalities in structure and function of the gastrointestinal tract underlie these disorders although the pathophysiology is poorly understood. Traditionally, FGID are diagnosed by excluding pathology in combination with careful examination and history taking[23]. The recent ROME IV documents outline in detail the symptom criteria required for diagnosis. Included under the umbrella of FGID are irritable bowel syndrome (IBS), functional constipation, functional diarrhoea, functional bloating, and functional dyspepsia to name but a few[24]. This thesis will predominantly concern gastroparesis and functional dyspepsia, IBS, functional constipation and defaecation disorders.

There was frequent debate as to whether FGID are a diagnosis of exclusion, where comprehensive investigations should be undertaken to ensure organic disease is not missed[25], or a positive diagnosis made based on symptoms. Generally in the community, the former appears to be the more commonly used, although this approach may lead to unnecessary expense[26]. There are now extensive data that show a diagnosis of FGID is stable over time and can be confidently made based upon symptom criteria and simple investigations. In its latest recommendations, the Rome Foundation favours a positive diagnostic approach to FGID, rather than making a diagnosis by exclusion[27].

Symptoms in FGID are likely to be secondary to mechanisms such as visceral hypersensitivity, motility disturbances, a change in gut microbiota and altered central nervous system processing, all of which involve dysfunction of the gut-brain interaction[27]. In clinical practice, patients often meet criteria for more than one FGID. Because of the marked heterogeneity of these disorders, the therapeutic approach has been often empirical in nature, therapies being instituted based on predominant symptom rather than defined pathogenic mechanisms.

1.2.1 Specific functional gastrointestinal disorders pertaining to this thesis

1.2.1.1 Irritable bowel syndrome

Irritable bowel syndrome (IBS) affects approximately 15% of the population. Its diagnosis is currently based on the presence of specific symptom criteria as defined by the ROME IV criteria (Table 1.1)

Table 1.1 Rome IV criteria for a diagnosis of IBS (based on Mearin 2016)[28]

Recurrent abdominal pain at least once a week over the last 3 months with onset more than 6 months prior to diagnosis. Abdominal pain is associated with at least 2 of the following: • Defaecation • Change in stool type • Change in frequency of defaecation

There are frequently other clinical symptoms associated with IBS such as abdominal bloating or distension, a sense of incomplete evacuation and passing mucus. However, these do not form part of the diagnostic criteria as they are not specific to the diagnosis of IBS[23]. IBS historically has been broken down into subgroups, such as constipation-predominant, or diarrhoea-predominant IBS. However, as patient symptoms can vary significantly over time, it is now understood that subtyping is descriptive of the symptom pattern in an individual at that time only[27]. Many patients move between various subtypes and functional diagnoses with disorders thought to exist on a continuum (Figure 1.1). For example, IBS often overlaps with functional constipation and may also include physiological subtypes of slow-transit constipation and pelvic-floor dysfunction[23, 29, 30].

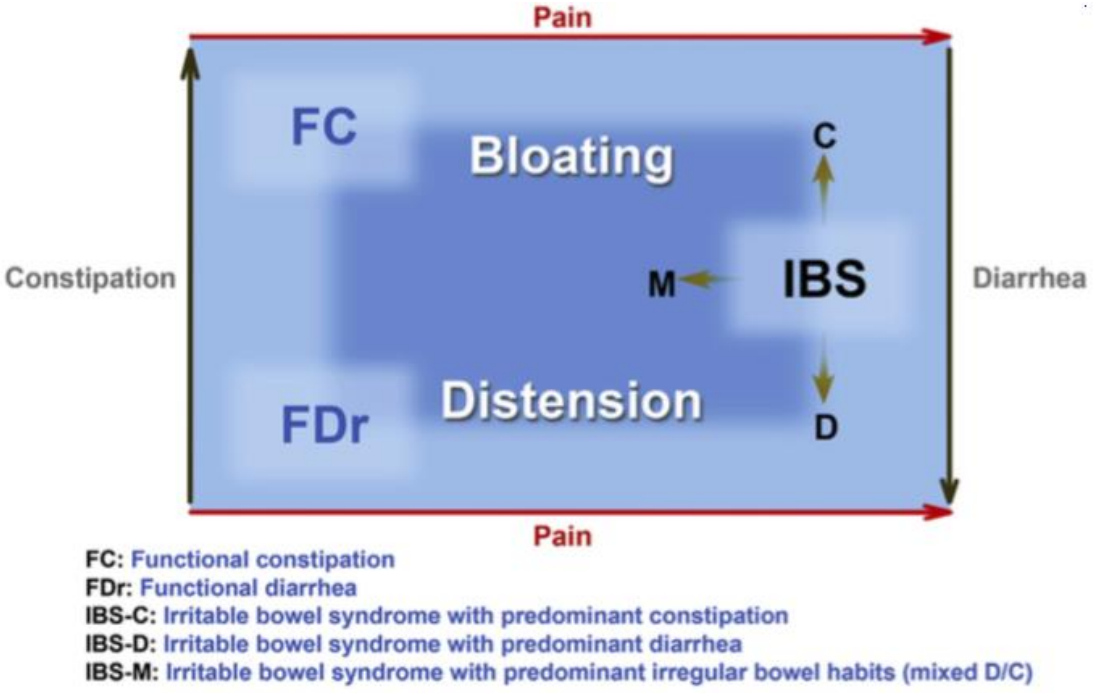

Figure 1.1 A conceptual framework explaining the overlap in functional gut disorders. Mearin et al, 2016, p1394. (with permission)

Multiple alterations of gastrointestinal structure and function have been identified in patients with IBS and other functional disorders. Although the overriding pathophysiology of IBS is largely still unknown, recent studies suggest contributing factors such as visceral hypersensitivity, altered gastrointestinal motility, altered immune processing, low grade inflammation, alterations in gut microbiota and aberrant stress responses along the gut-brain axis[31]. Furthermore, symptoms may be triggered by food intolerances, bile salt malabsorption, pancreatic insufficiency or psychological stress.

Visceral hypersensitivity is considered a hallmark of IBS. Studies have suggested that hypersensitivity to rectal distension is found in over 60% of patients with IBS [32, 33] where it remains a critical pathogenic mechanism in IBS. Hypersensitivity is associated with symptom severity[34], and potentially, increased pain perception may be associated with pathophysiological features associated with IBS such as immune activation with mast cell activation or altered neuroendocrine signalling to the brain[32]. In

some studies, episodic repetitive small bowel contractions and/or high amplitude propagating contractions have been associated with abdominal pain in patients with IBS[35]. In the normal gut, the ENS reacts to low-intensity stimulation via mechanoreceptors and chemoreceptors, and responds accordingly in gut functions of secretion, motility, blood flow. While normally the gut may respond to minimal stimuli, these are not perceived by the brain. However, in patients with IBS, the responses are exaggerated and may be perceived centrally as painful. This change in relationship between stimulus and perception seems to underlie visceral hypersensitivity[36]. The main receptor cells for chemical and possibly mechanical stimuli are the enteroendocrine or enterochromaffin cells, which then release serotonin, which acts on the primary afferents. Suggestions have been made that pain fibres in visceral organs are linked via afferent and efferent nerve reflex arches sharing painful stimuli, so-called viscero-visceral hyperalgesia[37, 38]. Another theory is that disruption to mucosal barrier function allows some microbiota to access extrinsic sensory afferents where both the presence of pro-inflammatory bacteria and mucosal immune dysfunction lead to visceral hypersensitivity and altered motility[39, 40].

The profile of gut microbiota is also altered in IBS. Normal gastrointestinal function including motility and sensitivity is closely related to the gut microbiome[41]. Higher colony counts of Clostridia and Bifidobacteria have been found in children with chronic constipation[41]. However, it has also been reported that patients with IBS have fewer Lactobacillus spp and Bifidobacterium spp detected in faecal samples than those with a healthy gut[42]. Nevertheless, a reduction in the diversity of gut microbiota and an increased ratio of Firmacutes to Bacteroidetes are commonly observed, but there is no other signature consistently reported for IBS[43]. Despite this, modulation of intestinal flora has become an attractive treatment appoach. A variety of ways of altering the gut microbiota in IBS have been studied, and these include ingestion of prebiotics, probiotics, symbiotics and antibiotics (such as rifaximin) with varying degrees of success[44]. Diet is another way of altering the gut microbiome. For

instance, reducing foods high in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) has been shown to reduce numbers of butyrate-producing and mucous-associated bacteria[44, 45].

Psychosocial factors influence not only the gut-brain axis and subsequent dysfunction, but also the patient's experience of illness and associated behaviours[27]. Emotions such as fear, anxiety, anger and emotional stress impact on the complex communication between the CNS and the gut, consequently affecting motility and sensation in the intestinal tract. As discussed above, CRH, the main mediator of the stress responses in the gut-brain axis, induces an increase in gut activity[3]. Psychosocial traumas such as childhood abuse are more common in patients with IBS than healthy individuals, and this can be associated with poorer clinical outcomes. Strategies such as validation of illness, the development of an effective therapeutic relationship between patient and clinician, and the employment of psychological management strategies such as gut-directed hypnotherapy and cognitive behavioural therapy contribute to more positive outcomes[27, 46, 47].

Psychological distress can lead to the activation of mast cells, which lead to the release of chemicals such as histamine as well as cytokines involved in the inflammatory process[48]. Biopsies of intestinal mucosa of IBS patients have found histological evidence of different cells involved in the inflammatory process such as T-lymphocytes, mast cells and neutrophils[3]. Post-infectious IBS is prevalent in about 10% people experiencing an infectious gastroenteritis suggesting the continuation of a low-grade inflammatory process.

1.2.1.2 Functional constipation

Chronic constipation remains one of the more difficult health problems to manage despite years of research into medications and numerous interventional strategies. It contributes a significant cost to

the economy, both directly and indirectly, affecting approximately 15% of the population in developed countries with up to 28% in the USA[49]. There is an increased prevalence of constipation among the ageing sector of the population, though the estimated figures are likely inaccurate, as there is the misconception among the population that it is a normal process of aging and subsequently some people are not seeking help[50, 51].

Functional constipation has been defined by the Rome Foundation. The latest criteria (Rome IV) are shown in Table 1.2. Symptoms of infrequency of defaecation, or evacuatory dysfunction must be chronic and loose stools should be rare without laxative use. Criteria for IBS must not be met[52]. However, it is recognised that patients can transition between functional constipation and IBS-C, which suggests these conditions should be seen as part of an overall FGID rather than locked into the one diagnosis[53]. There are a number of secondary causes of functional constipation some of which are outlined in Table 1.3.

Table 1.2 Diagnostic criteria for functional constipation as for Rome IV (based on Bellini 2017)[52]

For at least 25% of the time there must be 2 or more of the following

- Hard lumpy stools
- Straining to defaecate
- A sense of incomplete emptying on defaecation
- A feeling of blockage or obstruction
- Manual or digital assistance to evacuate

As well there must be less than 3 defaecations a week and:

- Do not meet criteria for opioid-induced constipation
- Do not meet criteria for IBS

Table 1.3 Secondary causes of constipation (based on Chatoor and Emmanuel, 2009)[54]

Structural	**Neurological**	**Myopathic**	**Other**
Tumour Stricture	Spinal cord injury Multiple sclerosis Parkinson's disease Aganglionosis	Systemic sclerosis Amyloidosis	Dehydration Immobility Pregnancy Diet

Congenital	**Medication**	**Metabolic**	**Psychological**
Hirschsprung's disease Imperforate anus Anorectal atresia	Opiates Psychiatric medication Cardiac medication Diuretics Parkinson's medicine Anticholinergics Oral iron supplements	Diabetes Hypokalaemia Hypomagnesia Hypercalcaemia Hypothyroidism Hyperparathyroidism	Abuse Eating disorders Affective disorders Chronic pain

There are four types of functional constipation: (1) Normal transit, or idiopathic constipation, where all investigation of colonic function is normal and includes IBS-C, (2) slow transit constipation, (3) evacuatory dysfunction with may be functional or structural and (4) a combination of both[55].

1.2.1.3 Normal transit (idiopathic) constipation including IBS-C

Normal transit constipation is basically as it sounds - constipation in the absence of outlet obstruction, but with a normal colon transit time. It may manifest as either chronic constipation or IBS-C. Although stool form is associated with colon transit time[23], there may still be infrequent, hard stools despite a normal transit time.

1.2.1.4 Slow transit constipation

Primary slow transit constipation is thought to be related to intrinsic colonic dysfunction either secondary to neuropathy or myopathy[56]. The condition is defined by the results of colon transit studies (see section 1.3.3)[18]. Motility disorders may affect any part or all of the GI tract[57]. Hence, patients with delayed gastric emptying may also have slow transit constipation[57, 58]. Slow transit constipation (STC) is more common in women, often affecting them in their younger and early adult years[59]. Patients with STC have ineffective colonic propulsion, due to inappropriate, weak or impaired propagating contractions[18]. There is also a reduction of response to normal stimuli such as sleep/wake and eating[20]. Aetiology is unclear but in some patients, depletion of neurons in the colon wall support the theory that an enteric neuropathy causes STC. Studies reporting a reduction in the ICC, the pacemaker cells of the gastrointestinal tract[60, 61], (Lyford, 2002; Rayner & Horowitz, 2012) support this[18, 62], where there is loss of enteric glial cells in the myenteric and submucosal plexus[63]. A reduction in the number of ICCs in the submucosa of the colon is associated with abnormal slow wave activity and reduced contractility[64]. The population of ICCs are also diminished in other conditions associated with gastrointestinal hypomotility, such as diabetic gastroparesis, inflammatory bowel disease and Hirschsprung's disease[60].

Delayed colonic transit may also be secondary to a functional defaecation disorder as a result of inhibitory neuronal feedback loops[65]. Nearly a 3rd of patients with rectal hyposensitivity also have slow colonic transit attributable to this process.

1.2.1.5 Functional defaecatory disorders

Defaecatory disorders include structural obstruction to defaecation due to anatomical changes such as rectocele, enterocele or intussusception, and functional obstruction due to poor propulsive force or inappropriate pelvic floor contraction (dyssynergia) during attempted evacuation[66]. The diagnosis

is made via balloon expulsion, anorectal manometry or defaecography, but, in experienced hands, a digital rectal examination is a good preliminary indicator of such disorders[66, 67].

Anatomical pelvic floor abnormalities, which may contribute to symptoms of constipation and incomplete evacuation include a rectocele, enterocele and rectal prolapse including intussusception. A rectocele is defined as an anterior herniation of the rectal wall forwards into the perineum/rectovaginal space[68]. It is commonly associated with multiparous women (seen in 40 to 70% of women), but rectocele is also reported in young nulliparous women[69, 70]. Symptoms occur when stool is trapped in the herniated segment often resulting in a sense of incomplete evacuation sometimes necessitating digitation or pressure on the perineum to facilitate defaecation[71]. Enteroceles are rarer, but do contribute to symptoms of obstructive defaecation, and are a herniation of the peritoneal sac which can contain small bowel, into the vagina or perineum[72]. Rectal prolapse, more commonly seen in elderly women, is the protrusion of all layers of the rectal wall through the anus[73] resulting from excessive straining and repeated injury to the pudendal nerve, or damage to the levator ani muscles, also contributing to intussusception. A rectal intussception is where the rectal wall inverts itself down towards the anus, sometimes descending into the anus, narrowing the intestinal lumen leading to obstruction[74]. This can be a result of lax uterosacral ligament support[75]. Conditions such as intussusception and rectocele also occur in men, however much less so, where frequently a physiological cause of these symptoms is not apparent.

Functional obstruction, in contrast, may be due to poor propulsion or inappropriate pelvic floor contraction, termed dyssynergic defaecation. Four types of pelvic floor dyssynergia are identified via standard anorectal manometry[76]. Type I is a paradoxical contraction or increased pressure of the external anal sphincter in the presence of an appropriate rectal pressure, whereas Type II has a poor rectal pressure or propulsive force combined with a paradoxical tightening of the anal sphincter. Type

III involves a failure of the anal sphincter to relax, maintaining a high anal pressure, but the rectal pressure is adequately increased, and Type IV is both a failure to relax, maintaining high anal pressure with no or an inadequate rectal pressure/propulsive force[76].

Altered rectal sensation is also likely to be important for defaecation, and rectal hyposensitivity is commonly seen in patients with constipation[65]. Whether rectal hyposensitivity is a cause or effect is still incompletely understood. Potential causes include mechanical injury to the pelvic nerves as in surgery, childbirth or trauma[65, 77], and constant distension of the rectum, which can lead to development of a megarectum[78]. Larger volumes are required for sensation, which may reflect the capacity of the rectum rather than disruption to neuronal pathways. The rectoanal inhibitory reflex (RAIR), important in preserving continence, is also impaired, requiring higher volumes of balloon distension to induce this response as seen in in manometric studies[79]. In total contrast, patients with faecal incontinence have a much-reduced rectal capacity, with a response to a small volume instilled into the rectum[80].

A number of patients experience an overlap of different mechanisms associated with constipation[63, 81]. For instance, patients with colonic neuropathy, as opposed to those with colonic myopathy, were likely to also have a type II dyssynergic pattern during evacuation, suggesting that there could be impairment in both colonic and rectal neuronal function[81]. Furthermore, rectal hyposensitivity may have an inhibitory feedback effect to the colon resulting in concurrent delayed colonic transit[65]. This has implications for management strategies.

1.2.1.6 Acute onset constipation

Constipation that occurs acutely in a previously un-constipated person or where its severity acutely worsens is very common and has multiple causes that might include dietary change, lack of exercise

(such as bed rest) and drugs. Its therapy and prevention are large topics, well beyond the scope of this thesis. The current discussion will, however, address one setting where constipation is a major, yet preventable problem – in hospitalised patients, particularly in the long-term care setting[82]. It is very common, with over 43% of inpatients developing constipation after 3 days of hospitalisation[83, 84]. Such a complication causes pain and distress, and contributes to increased length of stay and hospital readmission or emergency department visits. This has both economic and service delivery implications[83]. Contributing factors include immobility, malnourishment, dehydration and anxiety [85]. Medications such as anticholinergics, calcium-channel blockers, beta-blockers and opiates are also important contributors[86]. A particularly vulnerable patient group are those with a severe traumatic brain injury where persistence of faecal incontinence, frequently associated with constipation as overflow, is associated with a poorer outcome. Recovery of continence is more likely to have a more favourable outcome, where continence status affects rehabilitation outcomes[87]. As a result there is a need for consistent and appropriate management strategies in the hospital setting, particularly in rehabilitation, however barriers identified include a haphazard approach to bowel management and inconsistent documentation of bowel function[88, 89].

1.2.1.7 Gastroparesis and functional dyspepsia

Functional dyspepsia is a complex disorder characterised by a cluster of symptoms such as nausea, vomiting, belching post-prandial fullness and early satiety, abdominal pain and bloating, and has been defined by Rome IV criteria. (Table 1.4) In a proportion of symptomatic patients, functional testing reveals delayed gastric emptying in the absence of a structural gastric outlet obstruction, in which case the patients are referred to as having gastroparesis[90].

Gastroparesis may be caused by neuronal damage due to diabetes, viral illness, surgery and systemic neurological disorders (e.g., Parkinsonism)[14], although idiopathic dysfunction remains the most common cause[9].

Table 1.4 Identification criteria as per Rome IV for functional dyspepsia (Tack & Carbonne 2017)[90]

Must include one or more of the following in the absence of structural disease that have occurred over the last 2 months with onset > 6 months before diagnosis - Post prandial fullness - Post prandial early satiety - Epigastric burning - Epigastric pain Must also fulfil criteria for either PDS[1] or EPS[2]
[1]PDS – one or both of - Fullness impacts on daily activities - Early satiety prevents finishing a regular size meal [2]EPS – one or both of - Epigastric pain impacts on daily activities - Epigastric burning impacts on daily activities
Supportive criteria - Pain may be induced by a meal - Coexistent bloating, belching and nausea post prandially

[1] PDS, Post prandial Distress Syndrome [2] EPS, Epigastric Pain Syndrome

There are a number of potentially contributing mechanisms. Changes in duodenal function may be important with increased mast cells and eosinophils noted in the duodenal mucosa[90](Tack 2017). There may also be altered upper gastrointestinal microbiota. Gastric function is controlled by the

interaction between the ENS and ICC[9], and some symptoms, such as nausea and vomiting, are thought to arise from gastric dysrhythmias as a result of ectopic contractions arising from the ICCs[91]. There is also evidence of altered brain processing where MRI scanning has revealed changes in cortical thickness in some functional dyspepsia patients[90]. Genetic factors are also likely to be important, where different genotypes have been found between health and disease[90].

As mentioned above, delayed gastric emptying frequently overlaps with other dysmotility disorders involving the small bowel and the colon. It is thus not surprising that other aetio-pathogenic factors associated with this disorder include visceral hypersensitivity, gastric accommodation and psychosocial factors[92] highlighting the complex and intertwined nature of FGID.

1.3 **Clinical assessment, diagnostic tools and management strategies**

1.3.1 The importance of clinical examination

An accurate history and pertinent physical exam are important parts of the diagnostic process, particularly in the setting of abdominal symptoms and the possibility of FGID, where looking for comorbidities and/or medications that could affect bowel function are key elements[55, 66, 93]. However, it is equally important to develop a good rapport with the patient, as key patterns of behaviour are frequently not mentioned that would contribute to a more accurate diagnosis[66]. This approach is valuable also in identifying phobias associated with defaecation for instance and other psychological components, a history of physical or sexual abuse being all too common.

1.3.2 The role of investigations and utility of alarm symptoms

In patients with FGID, the presence of alarm features mandates that additional diagnostic tests be conducted in order to exclude organic disease[24]. Recognised alarm features include unexplained

weight loss, presence of fever, nocturnal bowel symptoms and blood in stools or melaena[39], as well as demographic features such as onset over the age of 50 years, and a familial risk of bowel cancer, coeliac disease or inflammatory bowel disease[94]. Frustratingly, alarm features are common and occur in up to 70% patients meeting IBS criteria[26]. In addition, certain alarm features have no obvious symptoms attached, such as asymptomatic anaemia, so the inclusion of simple, inexpensive blood testing, including complete blood count, coeliac serology, thyroid stimulating hormone and C-reactive protein, as well as faecal occult blood and stool culture for ova and parasites are often performed[26].

1.3.2.1 Differential diagnoses

As FGID are identified via a symptom-based diagnosis, it is important to exclude organic conditions. Some pathological conditions that require alternative treatments are easily missed[46]. There are differential diagnoses that may indeed be life-threatening as in colon cancer, or of organic origin requiring alternative management such as inflammatory bowel disease, and indeed, these have been found among people previously diagnosed with IBS[46]. Hence, patients exhibiting red flags warrant investigation, although the yield may be low[26]. (Black, 2012) Coeliac disease or microscopic colitis can be easily missed[95] as are pancreatic exocrine insufficiency and bile acid malabsorption. These all share symptoms of functional gut disorders[29] where being attentive to red flags and using simple investigations, as discussed further on, can increase this yield.

However, some benign organic or structural conditions that may trigger, exacerbate or perpetuate symptoms of a FGID may be overlooked. These include a range of anorectal disorders that commonly co-exist with IBS, such as faecal incontinence, functional anorectal pain and functional defaecation disorders[66]. In addition, concomitant or co-morbid conditions, such as depression and anxiety, endometriosis and pelvic floor dysfunction, may exacerbate or trigger symptoms in patients with IBS, and can be easily be overlooked[46]. These can have important implications for appropriate

management. Indeed, endometriosis and pelvic floor dysfunction will be addressed in detail in Chapter 4.

1.3.2.2 Pathology tests: blood and stool tests

Whether to order pathology tests in functional gut disorders has been an ongoing debate. The most recent Rome IV criteria currently states that diagnostic tests are not needed to diagnose IBS[28]. Nevertheless, in practice, testing often occurs. The presence of "red flag symptoms" in patients with IBS, should also prompt further testing[26], but the identification of pathology is often low. Routine tests ordered in practice include full blood count, C-reactive protein or erythrocyte sedimentation rate, coeliac antibodies, thyroid stimulating hormones, liver function tests and renal function, as well as faecal occult blood, ova and parasites and faecal calprotectin[24]. These tests may provide key information to support or exclude disorders suspected because of red flags, or differential diagnoses commonly associated with symptoms of IBS, such as coeliac disease and inflammatory bowel disease, which have a higher incidence in patients with symptoms consistent with IBS as compared to controls[95]. Faecal calprotectin is a useful test to discriminate between a gastrointestinal condition associated with inflammation and a functional one[35]. Calprotectin is a largely leucocyte-derived protein that is released into the GI lumen and is not degraded by gut bacteria[35]. Therefore, its presence at high levels in stools can be indicative of an inflammatory condition or a cancer in the GI tract. It is useful with a sensitivity and specificity of 93% and 94% respectively of excluding inflammatory disease when the level is less than or equal to 50 μg/g faeces. Testing for coeliac disease is recommended as the prevalence of coeliac disease in patients with symptoms of IBS is up to 4 times that of healthy controls[96].

1.3.3 Intestinal transit studies

Intestinal transit studies assess the function of the GI tract by measuring the time taken for a bolus to pass through its length. There are a number of techniques that may be employed.

1.3.3.1 Gastrointestinal scintigraphy

Gastrointestinal scintigraphic investigation requires the consumption of a radiolabelled meal and repeat gamma camera examination to record the passage of the labelled bolus overtime[92]. Scintigraphy can examine both whole gut and segmental transit. It is commonly used to confirm a diagnosis of gastroparesis or rapid gastric emptying. It is less commonly used to determine colonic transit time as multiple hospital presentations are required to complete the examination. The advantages of scintigraphy are that segmental transit can be assessed. The more commonly used labelling agents for a mixed liquid/solid meal are ^{111}In and diethylenetriaminepentaaceticacid (DTPA)[92]. Unfortunately, scintigraphy is time-consuming with some inconvenience to the patient, and exposure to repeated radiation[97].

1.3.3.2 Radio-opaque marker studies

A more convenient measure of colon transit involves the use of radio-opaque markers[18]. A number of protocols exist. Patients may ingest 10 radio-opaque markers for six consecutive days, and undergo plain abdominal x-ray on the seventh day. Alternatively, the Chaussade technique[98, 99] may be used where 20 markers are ingested on day 1 and 3, with a plain abdominal x-ray on days 4 and 7 to identify segmental differences in the colon. In clinical practice more simple methods are used such as the use of one x-ray 120 hours after ingesting 20 radio-opaque markers contained within a gelatin capsule[81, 100]. If there are more than 5 markers retained within the colon and/or rectum this is considered delayed transit. An alternative single x-ray method, that is said to increase the sensitivity of this test,

is the use of 3 different shapes of markers over 3 different days[54]. A single plain abdominal x-ray is taken on day 5, where an excess of any one group of markers indicates slow transit.

1.3.3.3 Wireless motility capsule (Smartpill)

A new innovative tool, the wireless motility capsule, "Smartpill" is a device that measures intraluminal gut pH, temperature and pressure as it passes through the GI tract[101]. By recording the different pH levels, it is possible to determine the different transit times; for instance, a sharp climb in pH indicates the passage of the capsule from the acidic environment in the stomach to the more alkaline duodenum. This tool, while accurate, is expensive, and its use has largely been restricted to research[102]. (Table 1.5)

Figure 1.2 An image of the wireless motility capsule.

Table 1.5 Normal transit times in the GI tract as per scintigraphy and the wireless motility capsule (Maurer 2006; Tran 2002)[57, 92]

	Scintigraphy	Wireless motility capsule
Gastric emptying time	30 mins – 4 hours	< 5 hours
Small bowel transit time	2 – 4 hours	4.1 hours (average)
Colon transit time	12 – 72 hours	59 hours (average)

1.3.4 Investigation of anorectal function

1.3.4.1 Anorectal manometry

Before one can plan appropriate management strategies, identification of the structural or physiological abnormalities of the anorectum associated with defaecatory disorders are essential. Assessment of the anal sphincter, anorectal, and pelvic floor coordination is conducted using anorectal manometry[103]. Recent advances, with the development of the more precise, high resolution anorectal manometry (HRAM)[76], have provided a paradigm shift in the ability to visualise pelvic and anorectal function, enhancing our comprehension of the pathophysiology of anorectal disorders. 3-D high-definition anorectal manometry (3D-HDAM), the latest iteration that shows a 3D perspective, involves the insertion of a rigid, sheath covered probe with 256 sensors into the anal canal with an inflatable balloon lying in the rectum[104]. Examination protocols generally include:

- an anal resting pressure over a 20 second period
- 3 squeeze manoeuvres (contracting the external anal sphincter over a sustained 20 second period)
- three individual cough responses, to assess involuntary contraction of the anal sphincter vs voluntary, followed by
- 3 evacuation attempts representing defaecation.

The RAIR is then assessed by the insertion of 30 ml, and if necessary 60 ml of air into the balloon. Rectal sensory testing follows by the gradual inflation of the balloon recording at what volume the first change in sensation is noted, followed by the first urge to defaecate, then the maximum tolerated volume[76, 104]. This diagnostic tool is valuable in being able to confirm suspected dyssynergic patterns and in diagnosing anal sphincter weaknesses. There are some limitations to the test. The fact that patients are supine possibly creates some false positive results which need to be considered, where it was found over 60% of healthy controls show a dyssynergic pattern[105]. This percentage is reduced to 33% if the balloon at the end of the probe is inflated to 60ml, simulating presence of a stool. Furthermore, the probe has to be held in place by the operator which prohibits the more accurate position of sitting on a commode[105].

1.3.4.2 Defaecating proctogram

Assessment of rectal evacuation can easily be made via evacuating proctography which involves instillation of barium paste into the rectum followed by taking x-ray images while the patient is seated on a commode attempting to expel the contents[106]. This technique has the advantage of being able to examine real time evacuation, with excellent imaging of anatomical disorders, however it is unable to easily examine all 3 compartments, (bladder, vagina and uterus, and rectum) within the pelvic floor without some discomfort to the patient[107]. Defaecating proctogram magneto-resonance imaging (MRI) likewise assesses the same, with the advantage of not involving ionising radiation, but the patient is in a supine position, which is non-physiological[107]. Despite this, however, MRI defaecography is able to evaluate the 3 compartments at the same time and better detect structural and functional causes of obstructive defaecation[107].

1.3.5 Management strategies

The management of patients with FGID is a large topic and, because of the multiple factors that are involved in the pathogenesis of symptoms, it involves multiple modalities. A brief overview of therapeutic strategies for IBS and chronic constipation will be made followed by a more focussed review of newer approaches focussed on the pelvic floor and neuromodulation

1.3.5.1 Traditional management strategies for IBS.

The core principles of managing IBS symptoms involves a fourfold approach, namely 1) the development of a trusting therapeutic relationship between the health professional and patient so that the symptoms are validated. This includes education including concepts on the gut-brain axis how they might contribute to the patient's symptoms and their ability to manage their symptoms;[40] 2) dietary approaches, in particular the low FODMAP diet[36]; 3) psychological strategies[108]; and 4) pharmacological intervention[40]. (Chey 2015) The choice of a specific therapeutic approach is largely driven by the nature of the symptoms[109], since the effectiveness of most therapies are restricted to specific symptoms. Initial interventions have traditionally been over-the-counter remedies; for example, fibre supplements and/or laxatives are used for constipation and anti-diarrhoeal preparations for diarrhoea. Conventional drug therapies include laxatives, antidiarrhoeal preparations, analgesics, antispasmodics, antibiotics such as rifaximin, antidepressants and the serotonin agonists/antagonists[40].

Psychological therapies such as cognitive behavioural therapy (CBT) and gut-directed hypnotherapy (GDH) have shown efficacy in multiple studies[108, 110], but it is unclear whether they have any benefit over antidepressant therapies for patients with IBS[111]. GDH involves assisting the person into a relaxed state where suggestions are made repetitively to the subconscious via the use of metaphors to normalise gut function. This now has a large evidence base[47, 108]. This works on the gut-brain axis,

where gut responses to emotional or environmental factors impact on the reflex circuits within the enteric nervous system affecting the coordination of basic gastrointestinal function. There are no clear predictors of response to GDH and it appears to work across a broad spectrum of persons and personalities. CBT and interpersonal psychotherapy have also been described as being effective in treating IBS, where the use of education, with behavioural and cognitive techniques are believed to work on the gut-brain axis and reduce anxiety[110]. The placebo response rate is reported to be high with the supportive interactions and relationship that develops with the therapist[112].

Approximately 60% of people with IBS identify food as a trigger, mainly foods such as dairy, wheat and caffeine[113, 114]. In many centres, the low FODMAP diet has become a first-line management strategy in IBS targeting key symptoms of bloating, abdominal pain and diarrhoea. FODMAP, a collective name for Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols, describes slowly-absorbed and/or indigestible, but readily fermentable short-chain carbohydrates. Common FODMAPs in the diet include fructose (in excess of glucose), lactose, fructans, galacto-oligosaccharides and the sugar polyols, sorbitol and mannitol[113]. Dietary FODMAPs have osmotic effects in the small intestine (increasing the water content of the lumen) and are rapidly fermented by gut microbiota producing gas. Both of these effects contribute to luminal distension, which, in the hypersensitive gut, may induce pain, bloating, and secondary changes in gut motility[115]. Strictly reducing FODMAP intake significantly reduces symptoms of bloating and abdominal pain in about 70% of people with IBS[114], and most are subsequently able to reintroduce FODMAPs into their diets to a less restricted level while maintaining good symptom control. Strict restriction does appear to impact on the gut microbiota, particularly reducing those producing butyrate[45], but this is not an issue when reintroduction is performed and less severe restriction in maintenance is achieved[116].

1.3.5.2 Traditional management strategies for chronic constipation:

Management strategies for chronic constipation generally take a step-wise approach, with education on bowel habits and toileting, fluids, dietary fibre and exercise being first-line[17]. Supplementation with dietary fibre preparations, commonly psyllium and wheat bran, can be of benefit[117]. In patients with IBS-C, such approaches can be associated with unacceptable bloating and flatulence (even if introduced at low dose with progressive increases to the desired therapeutic dose). This relates largely to bacterial fermentation of fructans contaminating wheat bran. However, psyllium, which is slowly fermented[118], is better tolerated in patients with IBS-C, where wheat bran is ineffective, or even may worsen the condition[117]. For those unresponsive to dietary changes, lifestyle and fluid intake modification and additional fibre, further assessment may be required to identify possible contributing factors such as a defaecatory disorder, or slow transit colon[22, 55].

Laxative use is indicated when lifestyle and dietary modification, fluids, and increased fibre have failed, and generally commences with the osmotic laxatives[119] which can be used long term. The osmotic agents influence water retention in the lumen by creating an osmotic gradient. The osmotics are not degraded by bacteria being a large polymer, therefore minimising cramps and bloating[17]. Examples are Movicol or Osmolax (Polyethylene glycol)[120]. Stimulant laxatives, such as bisacodyl, a phenolphthalein analogue, or naturally-occurring anthraquinones such as senna, aloe, rhubarb and cascara, facilitate neurotransmitter release thus stimulating peristalsis[55]. They also stimulate the sensory nerve endings hence the common side effect of cramping and also thought to inhibit the absorption of water[121]. The anthraquinone derivatives are taken up by the enterocytes and likely to stain the colonic mucosa after prolonged use leading to melanosis coli, which is presumed harmless. Patients may find they need to escalate doses in order to achieve a bowel motion, but they are neither addictive nor cause rebound constipation when ceased[54, 122, 123]. In patients that have failed laxatives, prucalopride, a selective, highly affinitive 5-HT4 agonist[50, 122-124] may be beneficial. Prucalopride is

structurally different to other prokinetics and more selective for the 5-HT4 receptor with far less action on the other serotonin receptors than previous serotonergic agents. There are other agents such as lubiprostone and linaclotide[125] that have efficacy in large studies, but these have yet to be released in Australia. Lubiprostone acts on the chloride channels, thereby increasing levels of intestinal fluid, and Linaclotide also increases intestinal fluid and reduces transit times via activity increasing cyclic guanosine monophosphate (cGMP)

Suppositories and enemas are generally used in the patient who feels the urge to defaecate, but has difficulty doing so; a situation commonly seen in patients with pelvic floor dysfunction[121]. Commonly used suppositories include glycerine or bisacodyl suppositories, and enemas contain sodium citrate/sodium lauryl sulfoacetate/glycerol (Microlax) or sodium phosphate (Fleet enemas). Trans-anal irrigation, where water is delivered into the rectum via a tube attached to a cone or a hand pump, also appears to be a safe means of evacuating the rectum in patients unresponsive to other strategies[126].

One view is that non-response to simple first-line strategies indicates a need for biofeedback rather a trial-and-error journey through several laxatives or prokinetic agents, as commonly applied[121].

1.3.5.3. Biofeedback

Biofeedback, also known as behavioural therapy as a change in a patient's behaviour is the goal, involves education on defaecation techniques and education on the basic pathophysiology of defaecation[121, 127]. Specialised physiotherapists or nurses generally teach it. Predictors of success for this method include a diagnosis of pelvic floor dyssynergia, or outlet obstruction as the main contributor to constipation or a combination of this and delayed whole gut transit[128]. Biofeedback aims to teach the patient with a dyssynergic pattern of defaecation how to identify the sensations

associated with relaxing the anal sphincter and to correct misperceptions of volume of stool in the rectum that is required for a response[129]. Added to this is teaching the so-called diaphragmatic push effort, where diaphragmatic breathing is used to increase abdominal pressure to assist the pressure needed to evacuate a stool whilst relaxing the anal sphincter to allow passage of stool[127]. These techniques can be assessed by the insertion of a balloon or a probe via the anal canal into the rectum. Ideally, the balloon and probe are connected to an electromyography machine where the patient can observe the relaxing and contracting of the sphincter while performing as directed, and learning to associate the correct sensation with the correct visual image. However, being able to have this facility is not common[130]. Correcting rectal hypo or hypersensitivity does not benefit from visual assistance. To correct this, firstly the balloon is inflated in the rectum to levels where the patient initially describes the urge to defaecate. The patient is then taught in a coordinated, stepwise approach by repeatedly inflating the balloon towards the more appropriate volume, to recognise the call to stool at the desired volume[131]. Biofeedback has been shown to be superior over standard laxative treatments for efficacy in reducing symptoms of chronic constipation[127].

1.3.6 Neuromodulation

Since the discovery of electricity, it has been known that nerve fibres can be stimulated by an electrical current[132]. Electrical therapy was first utilised in Europe for neurological stimulation in the 19th century and possibly earlier in the Orient. Over the last 20 years, neuromodulation has been in use clinically, predominantly treating pain, tremor or spasticity. More recently, its use has been extended to many novel applications across cardiology, neurology, psychiatry, urology and, not least, gastroenterology. Neurostimulation of both the upper and lower GI tract have been around for some years now via a variety of methods, with several concepts of mechanisms of action that include central, autonomic, or enteric hypotheses proposed[133]. Given the putative role of alteration of efferent or afferent function of the enteric and extrinsic nervous system in patients with FGID, neuromodulation has

increasingly gained traction for treating functional gastrointestinal symptoms resistant to conservative treatments. The best studied of these is sacral neuromodulation (commonly known as sacral nerve stimulation) for faecal incontinence[134], and, less clearly, intractable constipation[135]. Other non-invasive and more economical neuromodulatory techniques have also been explored, such as pudendal nerve stimulation[136], posterior tibial nerve stimulation[137], magnetic stimulation of the sacral nerves[138], and, to a lesser degree, transcutaneous interferential current therapy[139]. A brief overview of established neuromodulatory techniques will be discussed further followed by a comprehensive examination of transabdominal interferential stimulation, which is a novel neuromodulatory technique that is the focus of the research described in this thesis.

1.3.6.1 Sacral nerve stimulation.

Sacral nerve stimulation (SNS) has varying degrees of success for patients with slow transit colon where it is thought to function by acting on a combination of central, motor and sensory neural pathways[140]. Sacral nerve stimulation is delivered via a percutaneous transforaminal approach, with the electrical current delivered directly to the sacral nerve roots known to control the pelvic viscera[103]. This is achieved via permanently implanted electrodes placed through the sacral foramen at the level of S2 to S4, connected to an implanted neurostimulator in a subcutaneous gluteal pocket[135]. While a number of studies have shown success in varying degrees in both constipation and faecal incontinence[135, 140, 141], this method is expensive and invasive, and requires 2 surgical procedures under general anaesthetic[142]. Given this, sacral nerve stimulation is not recommended as a first-line management strategy.

1.3.6.2 Gastric electrical stimulation

Neuromodulation of the upper GI tract is mainly via gastric electrical stimulation, more commonly known as the “Enterra” system, a model designed specifically for the stomach[15]. Two leads are

surgically placed in the antrum of the stomach and connected to a stimulator via an implanted receiver tunnelled under the skin in the same way as for sacral nerve stimulation. This can be done both laparoscopically or via laparotomy, the former less invasive and better for the patient, but more difficult, the open method easier for the operator. Naturally, selection criteria for patients undergoing such an expensive procedure – up to $60,000 - is strict[143]. Patients with diabetic or idiopathic gastroparesis need to have more than 7 vomiting episodes a week, show severe delayed gastric emptying on gastric emptying studies and are refractory to all other management strategies. The efficacy of gastric electrical stimulation is yet to be definitively determined; early results look promising where uncontrolled studies have shown positive results[144], but controlled studies suggest the effects do not appear to last, suggesting a placebo effect[145].

1.3.7 Non-invasive experimental management strategies

1.3.7.1 Posterior tibial nerve stimulation.

Posterior tibial nerve stimulation (PTNS) is a relatively new technique of neuromodulation used for a variety of conditions generally controlled by the sacral nerves such as bladder instability and incontinence, faecal incontinence and constipation[146]. It is thought that stimulation of the tibial nerve transmits impulses to the sacral nerves as the tibial nerve fibres originate from the2nd and 3rd sacral roots that innervate the bladder, the rectum and the pelvic floor. The mechanism of action may be similar to that of SNS as it stimulates the same nerve fibres[142], and indeed, a study showed both PTNS and SNS to provide similar benefits in the short term. However, the therapeutic benefit from PTNS was not maintained. The cost of SNS is high, with the estimated total cost to be about $32,775 about 4 to 5 years ago[147], whereas the cost of PTNS is more affordable, as well as not involving 2 surgical procedures and anaesthetics. The technique of using PTNS involves the use of a fine acupuncture needle inserted near the posterior tibial nerve at the medial malleolus of the ankle. This needle electrode is connected to the lead wire, as is an adhesive grounding electrode placed on the foot

where both electrodes connect to the device generating the current[137]. The current is turned on and increased until either a sensation is felt down the foot or a twitch is noted in the big toe. Generally, a patient has 12 half hour sessions over 12 weeks where improvement is usually noted by the 8th session. The therapeutic effect appears to last for some weeks to months after the last session where people return for a "top up" session[137]. This technique appears to work well with people with faecal incontinence, where several RCTs have shown a significant reduction in symptoms after treatment[148]. A pilot study showed promising results for its application in slow-transit constipation[146], but a placebo response could not be ruled out. A more recent study in its application for constipation[149] found no benefit regardless of its aetiology. It is a mystery as to why it works in faecal incontinence and not in constipation, as sacral nerve stimulation invokes the same nerve roots with very similar mechanisms of action[149]. The lack of success could be due to patients having to attend a clinic on a weekly basis for treatment, whereas SNS is available 24 hours a day, or whenever the patient chooses to turn the device on, it being implanted and regulated by the patient[149]. Further studies are needed, including the suggestion that patients be taught how to self-insert the acupuncture needle and manage their own stimulation.

1.4 Trans-abdominal interferential electrical stimulation

Interferential current therapy has been used for a number of years in a variety of settings including low back pain[150] and neurological disorders such as carpal tunnel syndrome[151]. More recently, interferential current therapy applied transabdominally has been reported to be effective in small studies in managing conditions such as faecal incontinence and constipation. It has the benefit of being completely non-invasive, cost effective and convenient, as it can be self-administered at home[152].

1.4.1 The nature of interferential current therapy

To stimulate the nerve of interest, the current has to pass through the skin and surrounding muscle to reach its target. This causes resistance to flow, requiring the use of higher current to achieve the desired result. Skin impedance is inversely proportional to frequency of current[153]. Low frequency currents, which are needed to stimulated nerves, result in high skin resistance. To overcome this, a higher current is needed, which can cause pain. In contrast, a high frequency current results in low skin resistance and passes through without pain[154]. Unfortunately, these currents are not suitable to stimulate nerves. Interferential current therapy hopes to overcome this dilemma. The use of interferential current therapy dates back to the 1950s where it was found that the use of an interferential current overcame or bypassed skin impedance that is usually experienced with low frequency currents, but allowed the benefits of a low frequency current to occur due to the development of an amplitude-modulated current within the target of interest[155, 156]. An interferential current is produced when 2 medium-frequency alternating currents that are slightly out of phase are crossed[157]. This new, modulated current is believed to be produced at the site of bisection of the 2 diagonally opposed currents by their interference with each other[158]. See Figure 1.2.

An interferential current can reach targeted deeper tissue if the target tissue lies on a diagonal path between the circuits outside the electrode border[158]. However, in reality, interferential stimulation is likely more complex. Interestingly, despite the growing popularity of interferential current therapy in various clinical settings, there have been few studies on its efficacy or its dispersion through body tissues.

The situation is further complicated by the fact there are 2 types of interferential currents: the “true” interferential current that is generated by the use of 4 electrodes and the “premodulated” interferential current that is generated within a device that delivers the currents and transmits via 2

electrodes only[158]. As would be expected, the true interferential current as opposed to the premodulated interferential current had the greater voltage recording at depth, showing superiority in efficiency of stimulation at deeper levels[158, 159]. With 'true' interferential current, the orientation and location of nerve fibres in relation to the electrodes affects whether the nerve fibres experience unmodulated or continuous, fully modulated, or partially modulated stimuli[160]. Orientation of the fibres along a current pathway results in zero modulation. Modulation that is more efficient occurs if fibres are oriented at the point of bisection of the stimulation axes[160]. How this translates to the stimulation of frequently mobile intra-abdominal structures is unknown. 'True' interferential current therapy is believed to have its maximal stimulation deep at the intersection of the two currents whereas premodulated may act superficially near the electrodes. Consequently, it is the 'true' interferential current that is recommended for use in abdominal or deep tissue[158].

A 4 kHz carrier frequency for the 2 currents has been found to more effective than 8 or 10 kHz in producing a hypoalgesic effect in back pain, and it is this setting that is frequently used in a variety of scenarios for interferential current therapy[158, 161]. At this frequency, it is claimed that there is better penetration through to deeper tissue while overcoming the problem of skin impedance.

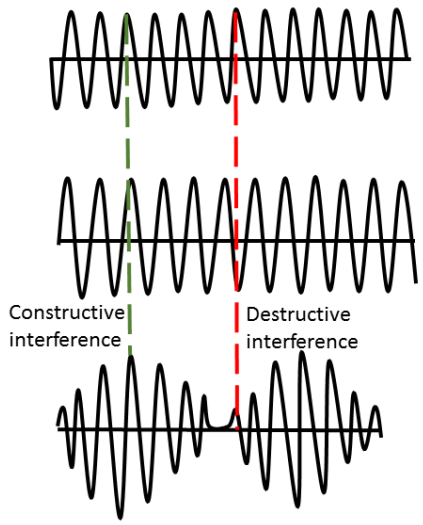

Figure 1.3 The interference of two sinusoidal currents of the same amplitude with with slightly different frequencies create the modulated current (bottom). Amplitude increase is caused by in phase constructive interference, whereas the out of phase destructive interference results in almost no amplitude.

(Adapted from Agharezaee & Mahnam, 2015)[157]

1.4.2 Potential actions of interferential current therapy

The mechanism of action of interferential current therapy in GI disorders is poorly understood. Whether it acts via stimulation of the ICC, the pacemaker cells of the gut, or stimulation of the enteric or extrinsic autonomic nerves has not been defined. However, as the given effects of stimulation are not immediate and last for some months after stimulation had ceased, they are more likely to be driven by alteration of neuronal function rather than by directly causing myogenic contractions[162]. It is conceivable that an interferential current may influence the neuroplasticity of the enteric nerves, inducing structural, intrinsic or synaptic changes leading to altered neuronal function. Certainly, neuroplasticity has been associated with motility disturbances in inflammatory bowel disease and IBS[163].

Interferential current causes increased propagating sequences and increased colonic activity[164], but evidence has yet to determine the precise mechanism of action. One potential hypothesis is that interferential stimulation exerts its effects via electrically stimulating excitable cells such as the ICC, which produce slow wave activity in the bowel responsible for peristalsis, or that it directly stimulates the nerves of the enteric nervous system[161]. Alternatively, because the placement of electrodes is in close proximity to the spinal cord, it is also suggested that its effects may be exerted directly to the spinal cord, influencing the autonomic (or extrinsic) nervous system either through the afferent or efferent pathways. It is feasible that, when used for bladder dysfunction, the sinusoidal current created by the interferential currents acted on the spinal cord around T12-L1[165].

There is also the possibility that hormonal systems are affected to explain the lingering effects after treatment. Increased endogenous levels of gamma-aminobutyric acid (GABA) and opioid agonists may also be induced by interferential current stimulation promoting anti-spastic effects for a short time[166]. This is supported by a case report of a patient taking concurrent tramadol who displayed the effects of opioid use such as drowsiness, decreased alertness and inability to concentrate for several hours after treatment by interferential current therapy[167]. It was hypothesised that interferential current therapy stimulated production of endorphins or enkephalins and that the additive effect of tramadol triggered this response. However, these theories have yet to be confirmed and indeed a placebo response has not been adequately excluded.

The placebo effect, that can be associated with the therapeutic alliance that develops with some practitioners, is frequently a confounder in assessing the therapeutic effect of such an intervention. In a study of patients with chronic lower back pain, active and sham interferential current therapy were compared in conjunction with either a limited (minimal interaction with the therapist administering the treatment) or an enhanced therapeutic interaction with participants (active

listening, demonstrating concerns) to examine the placebo effect[166]. The strongly positive response to active therapy with enhanced interaction was encouraging. However, the greater benefit of sham interferential current therapy with enhanced interaction over the real interferential current therapy and limited interaction was also enlightening. Certainly, a powerful influence of the therapeutic alliance was demonstrated[150] and future studies of this technique must consider the role of placebo. For instance, in a randomised controlled study of children with juvenile arthritis, half of the study group had combined interferential current therapy and resistive underwater exercises where the other half, as the control group, received traditional physical therapy alone and no underwater therapy[168]. The authors suggested that improvements in muscle strength and pain reduction was due to interferential current therapy theorised to be due to its actions on the local blood supply and suppression of pain-inducing chemicals. However, there is no direct evidence of this and it is entirely possible that the underwater therapy alone could have produced the same results; it was after all a novel therapy for these children, water being both less painful in which to move and more fun. Hence, this positive outcome may also have been secondary to the placebo response.

1.4.3 Non-abdominal use of interferential current therapy

Interferential current therapy has been tested against placebo in studies examining the pain response in healthy subjects [169] where interferential current therapy is known to significantly increase the pain threshold. It has been reported as a safe therapeutic option for a number of conditions with a variety of actions including analgesia, vasodilatation, and anti-inflammatory and sympatholytic effects. In addition, it may also stimulate circulation and promotes a decrease in interstitial oedema as suggested by a study examining its use in carpal tunnel syndrome[151, 170]. However, only 2 studies included robust objective measures such as electroneurophysiological indicators (sensory nerve conduction velocity) in carpal tunnel syndrome[151], passive range of movement in hemiplegic shoulders[170], and improved balance and gait in stroke victims[159]. (Suh, 2014)

Comparative studies with other types of stimulation such as action-potential simulation and transcutaneous electrical nerve stimulation have been conducted (Eftekharsadat 2015; Tugay 2007) where both types of stimulation were equally effective. Unfortunately, there were no placebo controls in those studies.

1.4.4 Urological uses

Patients with intractable back pain with concurrent bladder hyperreflexia who were being treated with interferential current therapy found their bladder symptoms improved. This led to a pilot study of 20 patients with multiple sclerosis in which the potential for an interferential current as a primary therapy for urological dysfunction was suggested by significant benefits demonstrated by objective cystomanometric studies[165]. In 2 other non-placebo controlled studies, significant improvement in enuresis, including nocturnal enuresis in children, and in general incontinence in the elderly were reported[171, 172].

Subsequently, 3 randomised controlled trials in children with differing bladder dysfunctions were published, all by the same research group. The largest study (n=54) was in children with nocturnal enuresis, in which a significant reduction of nocturnal enuresis (p=0.01) in the interferential current treatment group in comparison to a control group was demonstrated with no apparent adverse effects[173]. Efficacy was maintained for up for a year after therapy. The other 2 studies looked at the effects of interferential current therapy on urodynamic measures and continence in children with myelomeningocele and detrusor overactivity, and in non-neuropathic underactive bladder. All 3 studies showed improvement of bladder function ranging from an increase in bladder capacity and a reduction in enuresis to objective measures of urinary flow, flow curve and voiding time[174, 175]. Interestingly, the study of children with myelomeningocele and detrusor muscle overactivity (n=30)

noted that diarrhoea was a side effect reported the day after commencing therapy. It was this finding that led to interest in interferential current therapy as a treatment for bowel dysfunction[164].

1.4.5 Gastrointestinal application in children

The majority of studies on the application of transcutaneous interferential current therapy for constipation have arisen from Melbourne, Australia where several studies on children with slow-transit constipation have been conducted[152]. Chronic constipation remains a difficult condition to treat and children refractory to traditional treatments face surgical procedures such as appendicostomy or colectomy.

Results from the first pilot, "proof-of-concept" study on interferential current therapy in children were published in 2005[139] with findings supporting neuromodulation via interferential therapy improved colonic function. Eight children with severe constipation, of whom 7 had significant soiling problems, were treated by a physiotherapist. Three children had appendicostomies. The application of interferential current therapy to the lower GI tract was via placement of 2 electrodes on the abdomen lateral to the umbilicus and 2 on the back at the level of T9-L2. Leads were connected from the right front to the left back and vice versa so that the currents crossed[152] (Figure 1.3) Participants received between 9 and 12 stimulation sessions over a 4-week period[139]. Soiling disappeared in the first 2 weeks after interferential current therapy in 6 of the 7, although long term effects were less impressive. Constipation was considered resolved in 7 of the 8 children.

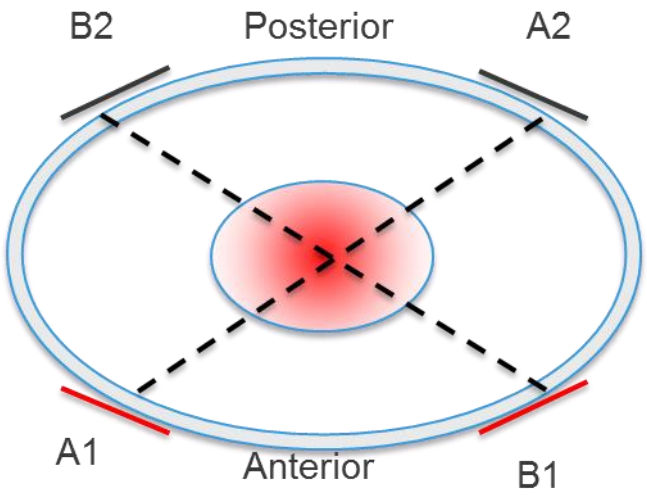

Figure 1.4 Pathway of interferential currents showing the positioning of electrodes on the abdomen and the creation of a third current at point of bisection inside the abdomen

The success of this pilot study led to other studies over the next few years with children randomised to receive actual or placebo treatment. Three studies involving children from this larger randomised controlled study reported on different outcome measures. The effects of interferential current therapy on propagating sequences was reported on a sub-group of children (N=7) who had an appendicostomy and were able to undergo 24-hour colonic manometry. These children had an increase in the frequency of antegrade propagating contractions with manometric patterns improving to lie in the normal range[152, 164]. Nuclear transit studies in some of these same children showed an improvement in transit time. However, it was found that those with concurrent upper gastrointestinal dysmotility did not respond as well to interferential current therapy compared with those participants with slow transit colon and normal upper gastrointestinal motility[176]. As a response gradually appeared over time rather than instantly, it is possible that the improvement in colonic transit times and increased propagating sequences were due to changes to the neuronal circuits rather than causing direct contractions of intestinal muscle during stimulation[164].

The advent of small, hand-held interferential devices enabled parents and children to be taught how to use the device at home. As a result, studies with larger groups of children, randomised to a longer, more frequent placebo or real stimulation (such as an hour a day daily for 3 to 6 months) were conducted[177, 178]. Outcome measures over these different studies included soiling, defaecation frequency, urge to defaecate, quality of life and objective transit studies. Again, there was a significant improvement in varying degrees to all, though quality of life indicators showed a modest, but statistically significant improvement as reported by the children, but not by their respective parents[179].

There are some concerns with the quality of the single institution studies discussed above. The main concern is that the reporting of different outcomes on the same group of children across several different studies creates an artificial impression that the number of studies conducted is higher than it is and it is difficult to tease out whether the overall outcome measures were met.

Nevertheless, the technique has been investigated further in different centres with some success. Thirty Iranian children with neuronal bowel dysfunction from myelomeningocele participated in a randomised controlled trial based on studies from the Royal Children's Hospital in Melbourne[180]. Constipation, as determined by stool form, decreased and the neurogenic bowel dysfunction scores improved from 'moderate' to 'mild' in the interferential current therapy group. These results were noted at 6 months after receiving treatment with an overall improvement in 73% of the children in the interferential current therapy group. In this group, it was suggested that the therapeutic action maybe more than just improved colonic transit time and it was postulated that pelvic floor muscle fibres may be strengthened or that there may be neuromodulation of the sacral reflexes as seen in patients with urinary and faecal incontinence[180]. Anorectal manometric indices also improved with a

significant reduction in both sphincter pressure and the recto-anal inhibitory reflex although it is not clear what the clinical significance of these are, as normal reference ranges are still debated[130].

Two recent studies have explored the efficacy of interferential stimulation in conditions related to anal sphincter function. One study hypothesised that placement of electrodes over the lower abdomen and sacral nerves would better assist with outlet obstruction or defaecatory dysfunction. Intriguingly, not only was there an increase in defaecation frequency and reduction in faecal incontinence in the majority of children, but the 2 with delayed gastric emptying had a demonstrated decrease in gastric emptying time[181]. This would suggest an effect in an organ that lies outside the area of stimulation. This may be because of the heterogeneity of biological tissue affecting the pattern of current flow[158], effects on the autonomic nervous system overall or mediation via enteroenteric reflexes. In another very recent study in children post-surgery for Hirschsprung's disease, interferential treatment plus behavioural therapy was more successful than behavioural therapy alone in normalising stool form, reducing incidences of faecal incontinence and increasing frequency of defaecation[182]. Nevertheless, success may well be attributed to the placebo effect. While use of the device with a sham current would be ideal, a true sham stimulation has yet to be found.

Few studies have explored the use of interferential stimulation in the treatment of other gut dysmotility disorders in children. As discussed before, intriguingly, children with slow-transit constipation and normal upper gut transit responded to interferential current therapy, whereas those with concurrent upper gastrointestinal dysmotility did not. The more recent finding of an improvement in gastric emptying time in children with delayed gastric emptying and constipation were those who had rectal or colonic distension as the cause of constipation, not slow transit[181]. This was, however, only 2 children, and formal randomised controlled trials studies have yet to be conducted.

Another recent study was conducted in children who had a combination of bladder and bowel dysfunction where education, diaphragmatic breathing exercises and behavioural modification alone were compared with a group with additional interferential current therapy[183]. Both bowel and bladder symptoms improved in those receiving interferential current therapy, a not surprising finding because innervation of the bowel and bladder derives from the same sympathetic and parasympathetic nerve fibres including the sacral nerves, where electrical stimulation of these is now thought to enhance function[182].

1.4.6 Gastrointestinal application in adults

There have been a handful of studies exploring interferential current therapy in adults with constipation. The first was a pilot study conducted in France on 11 patients with proven slow transit constipation[98]. Participants used interferential current therapy at home for an hour a day for 3 months. Primary outcome measures were the number of bowel motions a week and validated constipation questionnaires completed before and after the 3-month period. Seven of the 11 significantly improved in all scores and there was a slight, but statistically significant improvement in colon transit times at the end of the 3 months. Pre-stimulation, the majority of had a median number of stools per week of 0.66 and the highest post-stimulation frequency was 1.66 stools per week, results that might be regarded as clinically marginal. In addition, as there was no control group, it is possible that the improvement could be attributed to the placebo effect, particularly since the greatest improvement was in quality of life, a subjective outcome measure. As there was an improvement in colon transit time, it was suggested that parasympathetic nerve fibres were being stimulated, but it was a quantitatively small improvement[98].

The second study was a randomised control trial in 28 women who met at least two of the six Rome II criteria for constipation[184]. All treatments were performed by a therapist for 20 minutes a day, three times a week for four weeks. The placebo intervention (n = 14) appeared to receive the same treatment as the therapeutic arm (n = 14) with the exception that the stimulator was not actually switched on (i.e., they received no current). The outcome measures were a visual analogue scale assessing severity of pain, a constipation assessment score and the number of defaecations per week. Overall, the average number of defaecations per week improved from 3.7 to 5.6 in the treatment arm, but not in the placebo group. Stool form or the number of complete defaecations per week was not captured[27]. There was a high placebo response rate with the constipation assessment scale and pain scores improving significantly in both groups, although there was a greater improvement in the treatment arm compared to sham. The authors do note the lack of objective measures as a limitation, as well as the small sample size[184].

Another 2 studies were reported by a Turkish research group exploring the use of vacuum interferential current therapy in adults with IBS or functional dyspepsia. Both were randomised, blinded, placebo-controlled trials. Sham stimulation was the absence of any current, but suction cups were placed according to the study design, and still connected to the stimulating machine in the same way as active therapy, but not switched on[185, 186]. In both studies, treatment was administered by a physiotherapist 3 times a week for 4 weeks. Unfortunately, neither study had physiological outcome measures, but were restricted to symptom and quality of life scales. A strong placebo response was noted in both studies with no clear difference between the significant improvements from baseline in the real or placebo arms[186]. There was also a moderate participant dropout rate, possibly related to the exclusion of rescue medication. In addition, each study was at risk of responder bias as the questionnaires were administered by the study physiotherapists. Furthermore, the method of applying the electrodes in a quadripolar method on the back, rather than abdomen and back for those

with functional dyspepsia, does not fit with the suggestion that the area for treatment should be on a diagonal path where the currents cross at right angles[158]. In this study, their leads were all on the 1 plane, which contrasts to previous reports of the transabdominal approach where 2 electrodes are on the abdomen and 2 on the back, and the currents cross diagonally through the abdomen[139, 152]. This may have affected the outcomes. As results were presented as the number of patients who reported improvement not as individual scores, overall effect size is not clear. A further recent study on the application of transcutaneous electrical stimulation to the sacral nerves for constipation also applied electrodes on the same plane but over the sacral region[187]. It is entirely possible that their failure to achieve significant effects also related to the lack of intra-abdominal cross currents.

There have been other reports of success with gastric electrical stimulation for gastroparesis, but generally these are studies have involved the surgical implantation of devices such as Enterra therapy[133] and not of transcutaneous interferential therapy.

Table 1.6 Studies on interferential current therapy (IFT) and the gastrointestinal system

Author & year	Study purpose	Study design	Participants	Outcome measures	Intervention, frequency, duration	Results
Children						
Chase et al, 2005	Effect on constipation and soiling	Pilot study open label	8 children with slow transit constipation	Bowel diary pre, during, 1 & 3 months after – Soiling, number of washouts, medications	Physiotherapist given IFT 3/week, for 3-4 weeks	Soiling ceased, spontaneous defaecation increased, need for washouts ceased
Clarke et al, 2009	Effect on transit time	Placebo controlled RCT	26 slow transit children of a larger study group	Nuclear transit study pre, 2 months after RCT, and after open phase	Physiotherapist given IFT 3/week for 4 weeks, either placebo or real stimulation. All received active IFC for further 4 weeks	Colon transit time significantly faster following real IFT. No significant change in placebo
Clarke et al 2009	QOL after IFT	Placebo controlled RCT	33 children	QOL scores Parent and child before, and 6 weeks after treatment	Physiotherapist given IFT 3/week for 4 weeks, either placebo or real stimulation	Child score improved after real IFT but not placebo No difference in parental score
Ismail et al, 2009	Viability of self-managed home stimulation	Pilot study	11 children who previously failed earlier study	Bowel diary daily 1 month prior and after 2 months of stimulation	Home stimulation IFT 1 h/d for 2 months	Significant increase in defaecation

Leong et al, 2011	Long term effects	Follow up from RCT	39 children	Questionnaire via interview up to 4.7 y post	Physiotherapist given IFT 3/week for 4 weeks, either placebo or real stimulation	1/3 had improvement for >2 y
Yik et al, 2011	Effect in children with slow transit constipation and upper gut dysfunction	Subgroup in larger RCT	17 children in prior study	Nuclear transit study results as for other studies	Physiotherapist given IFT 3/week for 4 weeks, either placebo or real stimulation	Transit time did not improve in those with concurrent upper gut dysfunction.
Yik et al, 2012	Home stimulation trained by surgeon	Prospective	32 children	Bowel diary and Peds QL questionnaire before and during	Home stimulation IFT 1 h/d for 3 to 6 months	>3BMs week improved in soiling but not bowel action < 3 BM week improved in defaecation frequency

Clarke et al, 2012	Effect on propagating sequences	Prospective pilot study	8 children with appendix stomas	24 hr colonic manometry before and 2 months after	Physiotherapist delivered IFT 3/week for 4 weeks	Significant increase in propagating sequences. Half ceased washouts
Yik et al, 2012	Effect on appendicostomy rates	Retrospective	Children requiring appendicostomy	Retrospective review of operation and medical records	IFT stimulation as per studies	Appendicostomy rates dropped from 5.4 cases per year to 1.2
Kajbafzadeh et al, 2012	Impact on neurogenic bowel dysfunction in myelomeningo-cele	Placebo controlled RCT	30 children with myelo-meningo-cele	Bowel diary and anorectal manometry before and 6 months after therapy	IFT and placebo groups 3/week, 20 min session for 15 sessions	Significant improvement in symptoms, sphincter pressure and recto-anal inhibitory reflex, with IFT. Persisted in 53% for 6 months
Yik et al, 2016	Home IFT in children with anorectal retention	Pilot study	10 children with anorectal retention	Number of defaecations, episodes of faecal incontinence per week, stool consistency, PedsQL4.0, gut transit	Home IFT an hour a day for 3 months	90% children had increased defaecation frequency, decreased faecal incontinence, improved quality of life. No change in transit rate.
Zivkovic et al, 2016	Efficacy of IFT and DBE in children with bladder and bowel dysfunction	RCT	70 children with dysfunctional voiding and chronic constipation	Number of day and night time urinary incontinence episodes; UTIs, voiding and defaecation difficulties, defaecations and faecal	Group A: education + behavioural training + IFT 20 min, 5/week for 2 weeks Group B: education + behavioural training + DBE	Significant improvement in all outcome measures in children in group A only, except for uroflowmetry where no

				incontinence episodes per week, uroflowmetry	Group C: education + training only	indices changed in any children
Ladi-Seyedian et al, 2017	Effectiveness in children with post-operative Hirschsprung's disease	RCT	30 children with constipation and Hirschsprung's with no post-operative complications	Number of defaecations per week, faecal soiling, stool consistency, pain and constipation scores, anorectal manometry	IFT + behavioural therapy (n=15) vs behavioural therapy alone (n=15). Treatment 2/week for 15 sessions	Constipation symptoms improved and frequency of defaecation significantly increased in the group with IFT
Adults						
Koklu et al, 2010	Effect in functional dyspepsia	Placebo controlled RCT	44 adults with functional dyspepsia	Questionnaires given pre, during, at end of treatment & 1 month after	Physiotherapist applied vacuum IFT 3/week for 4 weeks	Statistically significant improvement in symptoms scores at both 2 and 4 weeks
Coban et al, 2011	Impact on IBS	Placebo controlled RCT	58 adults with IBS	IBS-GAI, VAS measuring pain, bloating, gas, incomplete relief after defaecation, IBS-QOL at baseline, end of therapy, a month after	Physician applied vacuum IFT 3/week for 4 weeks	Improvement in both IFT and placebo groups, but after 1 month in IFT group only

Queralto et al, 2012	Home IFT in adults with constipation	Pilot study	11 adults with constipation	Bowel diary, KESS, CCCS GIQLI scores and colon transit time before and after	Home stimulation IFT 1 h/d for 3 months	Significant improvement in bowel action, and scores from questionnaires
Yang et al, 2016	Effect on slow transit constipation in women	Placebo controlled RCT	28 women with slow transit constipation	Number of defaecations per week, Constipation assessment scale, VAS	IFT 20 min/day, 3/week for 4 weeks administered by therapist	Increased defaecation rate in treatment group, decrease in abdominal pain in both groups

Abbreviations: Randomised control trial – RCT; Quality of life – QOL; Paediatric Quality of Life - Peds QL; Bowel motion – BM; Irritable Bowel Syndrome Global Assessment of Improvement – IBS-GAI; Visual Analogue Scale – VAS; Knowles-Eccersley-Scott Symptom – KESS; Cleveland Clinical Constipation Score – CCCS; Gastrointestinal Quality of Life Index – GIQLI; Diaphragmatic Breathing Exercises -DBE

1.4.7 Overview of interferential therapy for constipation

The majority of studies of interferential therapy for faecal incontinence and constipation have been conducted at a single centre only and, while results from the Melbourne group appear as though many children have been studied, a lot of reports are from the same group of children. It is plausible that this could also be the same for studies arising from Iran[174, 180] as it is unclear whether the same group of children were the subjects of at least two of the papers. There were some differences in study design such as home stimulation for some children or physiotherapist-administered stimulation in hospital, or a variety of outcome measures. While this did not appear to impact on results of the various studies, it is clear an evolutionary pattern in the use of interferential current therapy in children is occurring as its acceptance in clinical practice grows. Overall, the benefits lasted from between 6 months and 2 years[188], and children who have since relapsed have gone on to continue home stimulation with ongoing benefit.

The theory that interferential current therapy works by creating a third therapeutic current at the point of bisection is appealing in that it targets places that have previously been relatively in accessible. However, exactly what happens is hotly debated[157]. The heterogeneity of skin, muscle and other tissue means an uneven resistance to electrical currents reducing the predictability of penetration of the interferential current[158]. Nevertheless, numerous studies have found it to have benefit with several studies using a placebo-controlled group. However, this is difficult to accomplish as sham stimulation so far has been applied via no current passing between electrodes with the participant being told that the current is subsensory[162, 180]. This may be convincing in children, but adults are possibly less likely to accept no sensation as still having a therapeutic effect. These studies also required participants to come in to the clinic for treatment, which also makes it easier for an investigator to create a realistic sham scenario, whereas more recent devices are small enough for patients to take home and use[178]. This has implications for a sham control by this means. The moving

of electrodes away from the therapeutic target and non-crossing of currents have been suggested as possible sham, but, as the actual predictability of current behaviour in human tissue is still unknown, it is possible some therapeutic benefit may occur and, coupled with the placebo effect, this may affect such studies.

In conclusion, there is speculative evidence that interferential current therapy is a viable alternative in reducing symptoms of constipation and faecal incontinence, as well as being attractive in the fact that it is of relatively low cost, and is a non-invasive and non-pharmacological intervention. (Hutson 2015) As the majority of studies on its use in constipation and faecal incontinence have been conducted in children, more adult studies are needed, in particular placebo-controlled studies. An effective means of delivering a placebo current still needs to be identified, as comprehension on the exact distribution and effects on deeper tissue is still limited[158]. Such challenges have been undertaken in Chapters 6, 7 and 8 of this thesis.

CHAPTER 2: –AIMS AND HYPOTHESES

Identification of functional disorders of the gastrointestinal tract, whether acute or chronic, is generally straightforward, particularly if principles of diagnosis as defined by the Rome Foundation are followed. However, making the diagnosis can be challenging in many patients where there is an overlap of symptoms both within functional disorders or other disease processes[28]. This can be of particular concern when appropriate management strategies are subsequently missed. Management of functional problems also offers challenges. This is evident in the approach to constipation of acute onset in hospitalised patients where medications and inactivity increase the risk of it complicating the admission. Management in this setting is frequently ignored until the problem becomes major, leading to delayed treatment and unnecessary morbidity. Chronic constipation has multifactorial causes that include slow colonic transit and pelvic floor dyssynergia, but therapy remains unsatisfactory in many patients. Novel, non-pharmacological approaches are needed for such chronic conditions with morbidity but no mortality. The current thesis aims to explore some key aspects of these issues, including diagnosis of FGID and associated conditions, early management of acute constipation in a high-risk setting, and the application of a novel neuromodulatory technique in patients with chronic upper and lower gut motility disorders.

2.1 Chapter 4: Use of additional red flags and simple investigations improves identification of alternative therapeutic targets in patients presenting with irritable bowel syndrome.

Problem: While IBS should be readily identified in the primary care setting, alternate diagnoses and concurrent conditions that require other management strategies are easily missed in the absence of screening for red flags or the performance of an adequate physical examination.

2.1.1 Aims

- To determine if a nurse-implemented, protocol-driven assessment is useful in the identification of alternate and concurrent diagnoses in women referred with a provisional diagnosis of IBS.
- To examine the association of pelvic floor dysfunction with symptoms of IBS and to identify predictors for pelvic floor dysfunction.
- To examine the symptom phenotype in women with IBS and concurrent endometriosis and assess the efficacy of a low FODMAP diet in this group

2.1.2 Hypotheses

- A significant number of women are misdiagnosed with IBS and that the use of a structured protocol with simple tests and appropriate physical examination identifies other conditions that would respond to alternative management strategies.
- Pelvic floor dysfunction is common in patients with IBS and the presence of particular symptoms predicts a positive clinical examination.

- Endometriosis and IBS both feature visceral hypersensitivity where the low FODMAP diet will reduce gut symptoms in women with endometriosis and IBS

2.2 Chapter 5: Evidence-based, nurse-led management of constipation in the hospitalised patient

Problem: Hospitalised patients are at an increased risk of developing constipation. However, it is not well managed, intervention generally occurring only when many days have passed and in an ad hoc manner. Overflow incontinence can result when faecal impaction develops. The location to which patients are discharged following rehabilitation for a traumatic brain injury is affected by continence status. Nurses are underutilised in strategies that can prevent constipation from developing.

2.2.1 Aims

- To identify current practice of constipation management in the Acquired Brain Injury Unit at Caulfield Hospital
- To identify current nursing culture around patient bowel care
- To identify impediments to effective management of constipation in the ward
- To implement and monitor an evidence-based bowel care plan for the prevention of constipation
- To measure the outcomes by comparing patient bowel chart data before and after the use of the care plan.

2.2.2 Hypothesis

- Implementation of an evidence-based care plan used by nurses will
    - reduce the incidence of constipation in the ABIU; and

- Be associated with consistently accurate documentation of patient bowel activity and laxative use in the electronic bowel chart.

2.3 Chapter 6: Transabdominal interferential electrical stimulation for refractory gastrointestinal motility disorders.

Problem: Patients refractory to management strategies for gastroparesis and/or constipation struggle to gain symptom relief, often requiring hospitalisation.

2.3.1 Aim:

- To determine the response of patients with refractory gastroparesis and/or constipation to transabdominal interferential electrical stimulation as an alternative therapy.

2.3.2 Hypothesis

- Patients not responding to traditional therapies for gastrointestinal motility disorders will report symptom reduction following 3 months of interferential therapy.

2.4 Chapter 7: Determining the effectiveness of transabdominal electrical stimulation in the treatment of female adult patients with constipation.

Problem: While there have been a number of randomised controlled studies done looking at the efficacy of interferential stimulation in children with constipation, few have been done in adults.

2.4.1 Aim:

- To determine the short and long term efficacy of transabdominal interferential electrical stimulation in women with constipation via a randomised placebo-controlled trial.

2.4.2 Hypothesis

- Interferential electrical stimulation is an effective means of reducing symptoms of constipation and improving quality of life in women with constipation.

2.5 Chapter 8: Identification of the mechanism of action and predictors of success of interferential electrical stimulation used to treat women with constipation.

Problem: If transabdominal interferential electrical stimulation is effective in relieving constipation, its mechanism(s) of action are not known. Such an understanding might enable better targeting of this therapy to patients with constipation.

2.5.1 Aims:

- To determine the effect of interferential electrical stimulation on colon transit times, ano-rectal function and rectal sensory thresholds in women with constipation.
- To identify whether patients with slow transit constipation or those with pelvic floor dysfunction will differentially respond to interferential stimulation.

2.5.2 Hypothesis

- In women with constipation, interferential electrical stimulation will
    - reduce colon transit times in those with slow colonic transit; and
    - normalise evacuatory dysfunction and rectal sensory thresholds.

CHAPTER 3: METHODS

3.1 Participants

Participants for the prospective studies in Chapters 7 and 8 were recruited through Monash University's website advertising clinical trials needing participants, through Monash University's gastroenterology website, via the Functional Gut and the General Gastroenterology clinics at The Alfred Hospital, and via fliers posted around The Alfred Hospital and at various private gastroenterology and dietitian practices.

Nursing participants in Chapter 5 were recruited from The Acquired Brain Injury Unit via the nurse educator. Nurses had to be registered nurses working in the unit at the time of the study.

Participants for Chapters 7 and 8 needed to be female aged between 18 and 75 years and have a clinical diagnosis of constipation as defined by a greater than 6-month history of less than or equal to 2 spontaneous bowel actions a week and at least 25% of the time experience at least one of the following symptoms: hard lumpy stools that are difficult to pass, a need to strain at defaecation, and a sense of incomplete evacuation after defaecation. Exclusion criteria comprised pregnancy or planning to become pregnant, constipation secondary to medications, endocrine, metabolic or neurological conditions, any serious medical condition, known or suspected organic bowel disease, megacolon, past surgery to the colon or rectum, past surgery to the spine that affect the sacral nerves, metal implants in the spine, an insufficient comprehension of English and inability to give written informed consent. Participants needed to be naïve to interferential electrical stimulation.

3.2 Ethics

The prospective studies in Chapters 5, 7 and 8 were approved by Alfred Research and Ethics Committee, Chapter 5 study number 300/16, and 7 and 8, study number 282/14 and the Australian and New Zealand Clinical Trials Registry for Chapters 7 and 8, number 366633.

3.3 Randomisation and blinding

Participants in Chapters 7 and 8 were randomised into one of two groups

- Group 1, where participants received actual stimulation via currents crossing right front to left back, and left front to right back; or
- Group 2, the sham stimulation, where currents passed through right front to right back and left front to left back. (Figure 3.1)

Randomisation for these chapters were via opening an envelope from a shuffled pile where the participant was blinded to the intervention. The operator teaching the use of interferential stimulation was not blinded for the purpose of instruction on technique of delivery.

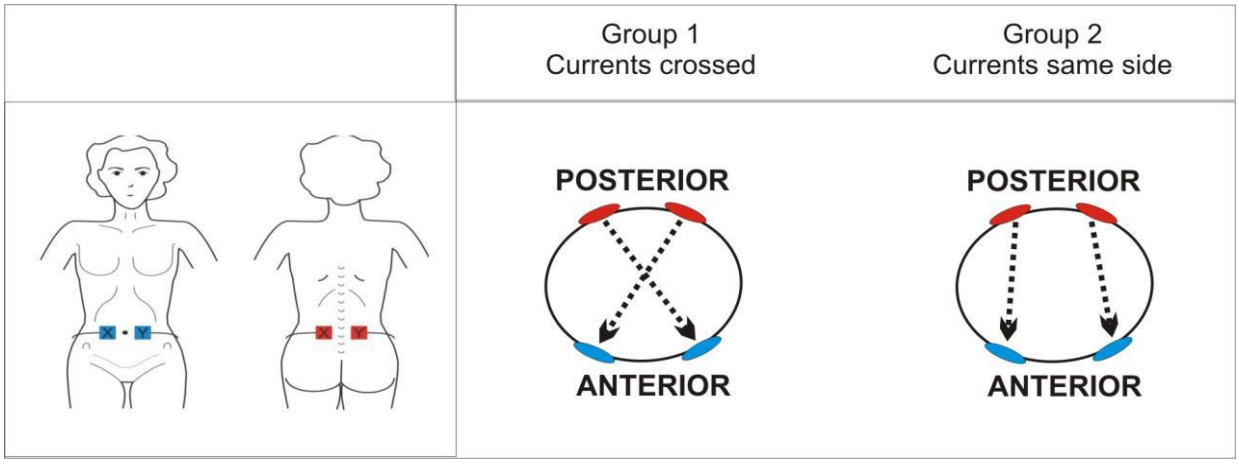

Figure 3.1Connection of electrodes for Group1 (actual stimulation) and Group 2 (sham stimulation)

3.4 Interventions

The interventions for Chapters 5, 6, 7 and 8 were as follows:

3.4.1 Evidence-based bowel care plan

The evidence-based bowel care plan for Chapter 5 was built on previously-developed protocols devised and implemented in similar situations[86, 189]. Based upon a literature review [66, 119, 190, 191] and consultation with the gastroenterologist responsible for bowel care in the unit, the laxatives of choice were Movicol, (Norgine Australia, Frenchs Forest, NSW), an iso-osmotic polyethylene glycol-based preparation, and a stimulant laxative, Dulcolax drops SP (Sanofi-Aventis). Both drugs are administered in liquid form and are, therefore, easily titrated. Several flowcharts were created and discussed in a working group consisting of a gastroenterologist, 2 nurses, a pharmacist and a speech therapist in the unit. An early version was reviewed and pilot tested in a hospital ward by nurses for ease of use. From feedback and dialogue, a final version was created (Table 3.1) and subsequently approved by senior medical, nursing and administrative staff at the unit.

This plan was charted by the ward doctors in the notes of patients deemed at risk of developing constipation in the ward. This intervention was designed so that nurses could easily follow, make their own decision about whether or not to administer a laxative according to the plan, document and follow up accordingly.

Table 3.31 Evidence-based bowel care plan[119, 190-192]

Assessment	No. of days	Nursing Intervention
Bowels not open	1	Continue standard care
	2	Medical review to eliminate impaction. Impacted: act as per instructions Not impacted: 1 Movicol sachet nocte
	3	1 Movicol sachet b.d. Dulcolax drops SP X 10 nocte
	4	Movicol sachet X 2 b.d. Dulcolax drops SP X 20 nocte
	5	Medical review
Bristol Stool Scale 1,2,3 Maintain at dose required to achieve type 4,5 unless type 6,7 occur	1	Movicol 1 sachet nocte
	2	Movicol 1 sachet b.d.
	3	Movicol 1 sachet mane, 2 sachets nocte
	4	Movicol 2 sachets b.d.
	5	Medical review
Bristol Stool Scale 4,5		**Normal routine care**
Bristol Stool Scale 6,7	1	Cease laxatives. Notify RMO* *(if >2 type 6,7 see gastroenteritis guidelines)*
	2	1.5 teaspoon Fybogel/psyllium husk in water Ensure adequate hydration
	3	Contact medical team for review Collect bowel samples for lab testing

*Resident Medical Officer

An acquired brain injury can lead to dysphagia. The risk of aspiration required exploration of the administration of Movicol safely as the recommended preparation is the mixture of 1 sachet of Movicol with 125 ml water (Norgine Australia). In routine practice, thickened fluids are provided in

ready-made containers for these patients in 3 strengths - mildly thick, moderately thick and extremely thick. As Polyethylene glycol (PEG) disrupts the bonding links formed by polysaccharide chains and hydrogen bonds in a thickened fluid when starch-based thickeners are being used, there is a risk that the thickened Movicol will lose its consistency. This may not be a problem when xantham gum (thickener 415) is used[193].(Carlisle 2016) A variety of experiments were conducted with both plain and flavoured thickened fluids in ready-made containers (Flavour Creations Pty Ltd, Acacia Ridge, Queensland). The resulting thickened Movicol maintained its thickness for all three consistencies. Thus, a protocol was developed (as shown in Table 3.2) and adopted by the hospital for general use.

Table 33.2 Protocol/instructions for making thickened preparations of Movicol using the 3 consistencies of "Flavour Creations" premade cups of fluid

Mildly thickened (nectar)[A]
• Use ready-made cup of thickened water or lemon lime flavour – 185 ml/190 g • Aspirate 60 ml of fluid with a 60 ml syringe – discard • Gradually whisk in one Movicol sachet • Test consistency with spoon test to ensure thickness maintained – (note, fluid will take on a cloudy appearance, which is why the flavoured drink may be more palatable) • Have patient consume within an hour
Moderately thickened (honey)[B]
• Use ready-made cup of thickened water or lemon lime flavour – 185 ml/190 g • Aspirate 60 ml of fluid with a 60ml syringe – discard • Gradually whisk in one Movicol sachet • Test consistency with spoon test to ensure thickness maintained – (note, fluid will take on a cloudy appearance, which is why the flavoured drink may be more palatable) • Have patient consume within an hour
Extremely thick fluid
• Use ready-made cup of thickened water or flavoured – 185 ml/190 g • Remove 60 ml, either by 6 level dessertspoons, or aspirate with 60 ml syringe • Gradually whisk in the contents of one Movicol sachet • Test consistency with spoon test to ensure thickness maintained – (note, fluid will take on a cloudy appearance, which is why the flavoured drink may be more palatable) • Have patient consume within an hour

Note: Ensure use of the **Flavour Creations™** thickened fluids. They are thickened with Xanthan gum (thickener 415) which does not lose its thickness when combined with Movicol, unlike those made with starch thickeners, where the consistency can become runny.

[A] Term used in speech pathology to describe mildly thick fluid

[B] Term used in speech pathology to describe moderately thick fluid

3.4.2 Transabdominal interferential electrical stimulation

The intervention used in Chapters 6, 7 and 8 was a hand-held device that, when connected to electrodes placed on the abdomen and back, delivered 2 currents that passed through the abdomen according to randomisation described above (Figure 3.1). Patients were taught to place the electrodes as shown in Figure 3.4 and how to use the device. The exact position of the electrodes varied according to their underlying condition. For constipation, they were placed just above the level of the umbilicus as shown in Figure 3.2. For those with gastroparesis the electrodes were placed higher up than shown below, just below the costal margins. They were instructed to increase the level of stimulation to a comfortable level only and use for an hour a day, around the same time of day. It was suggested they set themselves up with phone, TV remote or book, cup of tea and put their feet up for an hour.

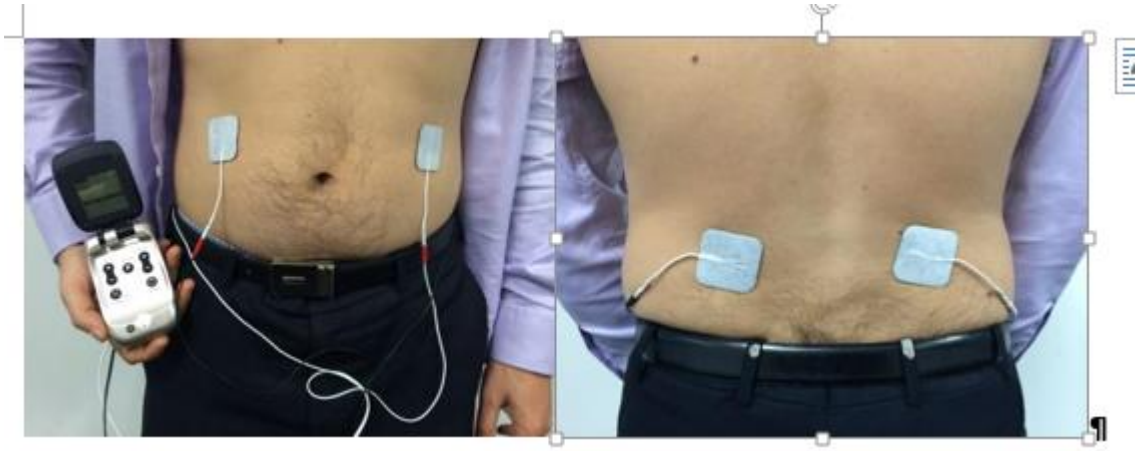

Figure 33.2 Location of placements of electrodes on the abdomen and back for treatment of constipation.

3.5 Measurements

3.5.1 Electronic bowel chart.

An electronic bowel chart is in use in the Acquired brain injury unit (ABIU) (Caulfield Hospital Melbourne) in advance of all documentation becoming electronic. Documentation of patient bowel activity via this system was gathered before and 3 months after implementation of the care plan. Specific data looked for included annotation of administration of laxatives in this chart, reporting of bowels not open (BNO) and stool type according to the Bristol stool scale. This data was captured for Chapter 5 to assess documentation.

3.5.2 Nurse questionnaire.

Nurse perceptions of the impact of constipation and confidence in management were assessed via a brief, 6-point questionnaire (Appendix 1). The first question asked if there was a management plan on the ward for managing constipation. Answers were a yes/no. The second question asked about frequency of checking patients' bowel activity. The remaining 4 questions used a visual analogue scale from 0 to 100 mm assessing their knowledge on the Bristol Stool Scale, perceptions on how constipation affects their work and its impact on the patient, and confidence in managing bowel care. Zero meant no impact, or not at all confident and 100 meant total impact or totally confident. On comparing a VAS score with a prior score, a change of 20 mm was arbitrarily deemed to be clinically significant. This questionnaire was created for and used in Chapter 5.

3.5.3 Gastroparesis Cardinal Symptom Index (GCSI)

The GCSI is a validated, quick 9-point questionnaire with a Likert scale, where 0 represents no symptom and 5 is worst possible symptom. (Appendix 3) Questions relate to the more common

gastroparesis symptoms. Participants in a validation study have found it to be easy to understand and use[194]. This questionnaire was used in Chapter 6 for patients with gastroparesis.

3.5.4 SF-12

The Short Form-12 (SF-12) is an abridged version of the well-known Short Form-36 (SF-36), a generic tool that can be applied to various population groups assessing quality of life[195]. This brief questionnaire was used in Chapter 6 for gastroparesis patients. (Appendix 4)

3.5.5 Patient Assessment of Constipation-Symptoms (PAC-SYM)

Measurement of patient's experience of constipation symptoms were gathered via the use of this 12-point questionnaire subdivided into abdominal, stool and rectal subscales where symptoms are rated on a 5-point Likert scale, 0 being no symptoms and 4 being severe[196, 197]. This validated questionnaire is frequently used in constipation studies and was selected for its simplicity. It was used in Chapters 6 and 7 at various time points.

3.5.6 Patient Assessment of Constipation-Quality of Life (PAC-QOL)

The PAC-QOL was administered at the same time as the PAC-SYM in both Chapters 6 and 7. It measures health-related quality of life parameters of constipation in 4 subgroups - physical discomfort, psychosocial discomfort, concerns, and satisfaction with bowel function. This assessment of 28 questions uses a 5-point Likert scale where 0 is none or not at all and 4 is extremely/all the time[198]. Five questions have the score answers reversed to avoid a floor or ceiling effect. This tool has been well validated and is used in a number of constipation studies. (Marquis, 2009)

3.5.7 Severity of bowel symptoms

Overall impression of severity of bowel symptoms over the prior 2 weeks was captured via a 100-mm visual analogue scale (VAS) where 0 was no symptoms and 100 indicated worst possible symptoms. A change of 10 mm or more was arbitrarily considered as clinically significant. This tool was used in Chapters 6 and 7.

3.5.8 Bowel diary

Participants in Chapter 7 were asked to keep a diary of bowel and laxative use for a 2-week period at various time points where they recorded daily the number of stools passed, how many were complete evacuations, the stool type based on the Bristol Stool Scale, how often did they strain or need to manually assist defaecation, and what laxatives were taken at what time. There was an image of the torso provided for each day on which participants were asked to shade where they felt the call to stool or other sensations associated with defaecation.

3.5.9 Colon transit study

Colonic transit was measured using radio-opaque markers study (Jem Medical GmbH Switzerland) where a gelatin capsule containing 20 biomarkers was ingested. Five days later, a plain abdominal x-ray was taken and the number of biomarkers retained within the colon or rectum noted[81]. More than 5 retained are thought to indicate a slow transit. Participants were asked to refrain from using any laxatives during this 5-day period.

3.5.10 Anorectal manometry

A 3-D high-definition anorectal manometry system (3-D HDAM Given Imaging) was used to obtain precise measurements of anorectal pressures[104]. A probe with 256 sensors covered with a disposable

sheath with a balloon for inflating on the end is inserted into the anal canal so that the sensors cover the length of the canal with a couple of groups of sensors just outside the anus, and at the proximal end that lie within the rectum. The patient is supine in the left lateral position and the probe is held in place by the operator. Anal sphincter manoeuvres are assessed as are involuntary reflex actions. Rectal sensation is assessed via gradual balloon inflation. Data are analysed via proprietary ManoView AR 3.0 software™ (Given Imaging)[199].

Rectal sensory threshold measures determined by gradual inflation of air in the balloon in 10 ml increments at the end of the manometry probe are:

- First constant sensation (FCS) – the volume at which a first awareness of a change in sensation in the rectum as the balloon is inflated is felt.
- Defaecatory desire volume (DDV) – the volume at the first urge that signals a need to defaecate is reported.
- Maximum tolerated volume (MTV) – the point at which inflation of balloon is uncomfortable. At this point the study is over and air is removed.

3.6 Statistical analyses

Results in Chapters 4 to 8 were expressed descriptively and analyses performed using Graph Pad Prism (version 6.00 for Windows, Graph Pad Software, La Jolla California USA). Categorical data were compared using Chi-squared or Fisher's exact test, and Odd's ratios calculated together with 95% confidence intervals. Comparisons of change within a group were analysed via a paired t-test, and comparisons between groups were via an independent t-test or Mann U Whitney test. Statistical significance was determined if the P-value was ≤ 0.05, except where Bonferroni correction was used for multiple comparisons.

CHAPTER 4 – IDENTIFICATION OF ALTERNATIVE THERAPEUTIC TARGETS IN WOMEN WITH IBS PRESENTING TO A NURSE-LED CLINIC

4.1 Background and aims

A number of alternate diagnoses that have symptoms that fulfil Rome criteria for IBS are known[200]. Frequently, patients are inadequately investigated[22], and such diagnoses may be subsequently missed. A number of comorbid and organic diseases exist with IBS where both a careful history and physical examination are needed to explore symptoms alongside the use of simple investigations[39]. "Red flags" serve to alert for more specialised testing.

While such a diagnostic process is relatively simple in theory, it has been identified that diagnosing IBS in primary care is challenging with both time and limited awareness around IBS, preventing appropriate identification and management[201]. One solution to this problem might be the use of appropriately trained advanced practice nurses who are in a unique situation with time and the ability to assess patients with IBS, exploring symptoms, assessing illness severity and identifying factors contributing to or inhibiting a positive outcome[202]. Patients have reported preferring to talk to nurses about their IBS symptoms as not only do they receive time and validation of their symptoms and fears, but also comprehensive education around their symptoms[46, 202].

Co-morbidities that have received relatively little attention in women with lower abdominal symptoms consistent with IBS are pelvic floor dysfunction and endometriosis. Since both may be amenable to targeted treatment that is different to standard therapeutic strategies for IBS, their recognition in patients with symptoms of IBS might be clinical beneficial. Symptoms or signs of these conditions are

not well represented in red flags. Furthemore, endometriosis, a common condition in about 10% of women of reproductive age, is itself associated with visceral hypersentivity[38]. Therapies directed towards visceral hypersensitivity, such as the low FODMAP diet, might be anticipated to be effective in patients with gut symptoms, but the association has not been examined.

The current study aimed to address the issues raised above. First, the utility of a nurse-led protocol for assessing and managing patients with suspected IBS referred by general practitioners, specialists and other health care providers, or self-referred for assistance in appropriate investigation and management strategies was examined by interrogating the database of a specialised private IBS service in Christchurch, New Zealand[46]. Secondly, it aimed to determine the contribution of a protocol that requires physical examination and investigation directed by red flags and by routine blood and faecal tests in identifying alternate and concurrent diagnoses in a female population referred with the provisional diagnosis of IBS. Thirdly, it aimed to examine the association of rectocele, a manifestation of pelvic floor injury and/or dysfunction, and endometriosis with IBS, together with historical clues to their presence. Fourthly, the study aimed to compare the relationship of the efficacy of the low FODMAP diet to a concurrent diagnosis of endometriosis in women with IBS.

4.2 Methods

4.2.1 Inclusion and exclusion criteria

Consecutive female patients attending the IBS service and who had completed a structured IBS symptom questionnaire (see below) were included in the study. Patients were excluded if they were lost to follow-up or failed to attend subsequent appointments.

4.2.2 Data collection

Data, collected prospectively over a five-year period (January 2009 to December 2013), were derived from a management protocol detailed in Figure 1, where the initial consult was conducted by an IBS nurse-specialist who took a detailed medical and symptom history. All patients underwent an abdominal and rectal physical examination, and provided a venous sample for complete blood count, iron studies, C-reactive protein, thyroid function tests, liver function tests, coeliac antibodies and kidney function, as performed by routine laboratory techniques. All patients sent stool samples for faecal microscopy and culture, and for faecal calprotectin by ELISA (Nova Tec immunodiagnostica GmbH, Christchurch New Zealand). A symptom questionnaire was given to the patient to take home, complete and return next visit. Results from this and the initial consult determined the processes for follow-up visits. This 40- question tool collected data that included onset and duration of symptoms, types of symptoms, triggers of symptoms and coexisting conditions utilising tick-boxes and visual analogue scales. All patients were classified as per Rome III criteria for IBS[23]. Red flag questions in the questionnaire asked about rectal bleeding, melaena, unexplained significant weight loss, nocturnal bowel symptoms, and pertinent demographics such as onset of symptoms over 50 years of age and a family history of bowel cancer. More intensive clinical interrogation, investigation and assessment by a gastroenterologist or colorectal surgeon were prompted by the presence of red flags and/or abnormal screening laboratory tests. A positive response to these elicited a referral for a colonoscopy if one had not been recently performed or appropriate referral on to another specialist. Other data collected included age, final diagnosis, presence of a rectocele, a prior diagnosis of endometriosis, or other additional diagnosis. Patients were defined as having endometriosis if diagnosed either prospectively or retrospectively via laparoscopy by a consultant gynaecologist according to referral information or noted on the questionnaire. A rectocele was detected by rectal examination by either the nurse specialist or colorectal surgeon. Alternate or additional diagnoses, confirmed by a colorectal surgeon or gastroenterologist, were linked to their questionnaire responses in an electronic

spreadsheet. Questionnaire data that included symptoms, coexisting conditions and medications were stored on a spreadsheet alongside age, final diagnosis, management strategies and ultimate outcome. The database was routinely prospectively entered in patient clinical care.

All patients with a confirmed diagnosis of IBS[203] were taught the low FODMAP diet by the nurse-specialist, who had been trained in the diet by an experienced dietitian, in a one-on-one session. Patients completed a food and symptom diary for a week prior. Their diet and symptoms were discussed, and education on implementing the low FODMAP diet given. Educational resources, the Monash University Low FODMAP Diet digital application for iPhone and Android[204] was recommended and the low FODMAP diet booklet[205] provided. The first follow-up visit occurred 4 weeks after initial instruction, when patients reported their experience with the diet. A positive response was defined as greater than 50% reduction in abdominal symptoms. Adherence to the diet was assessed by direct questioning where the patient reported either adherence all or most of the time, or non- adherence. Further instruction was given regarding reintroduction of FODMAPs in a gradual, systematic method according to individual responses, as per recommended guidelines[113]. Further follow up occurred as per individual needs.

For the purposes of this study, all data were contained in a locked data base and de-identified following which information was evaluated. Ethics approval was not required as this was a retrospective audit of anonymised data.

*Figure 4.1 Protocol for nurse-led clinic. *=Full blood count (FBC), Iron (Fe), C-reactive protein (CRP), Liver function tests (LFT), Urea and electrolytes (U&E), thyroid stimulating hormone (TSH), Microbes, culture and sensitivity (MC&S).*

4.2.3 Statistical analysis

Results were expressed descriptively and analyses performed using Graph Pad Prism (version 6.00 for Windows, Graph Pad Software, La Jolla California USA). Categorical data were compared using Chi-

squared or Fisher's exact test, and Odds ratios calculated together with 95% confidence intervals. Statistical significance was determined if the P-value was ≤ 0.05, except where Bonferroni correction was used for multiple comparisons.

4.3 Results

4.3.1 Patients

Between January 2009 and November 2013, 231 women attending the clinic met the inclusion criteria. Their demographics are shown in Table 4.1 according to whether or not they met Rome III criteria for IBS. Age differed by a median of 9 years between the two groups ($p<0.02$). Of the 187 with symptoms consistent with IBS, 114 (61%) reported red flags and 12 (6%) had abnormal routine investigation results in the absence of red flags.(Figure 4.1) Further investigations, including colonoscopy, revealed that 15 of those with red flags (13%) had alternative definitive diagnoses (8% of the initial IBS population). Thus, 160 women had a diagnosis of IBS, of whom 59 (31%) were identified with concurrent endometriosis, and 59 (31%) found to have a clinically important rectocele. Of the 44 who did not meet criteria for IBS, 28 met Rome III criteria for another functional disorder such as functional bloating (Figure 4.1).

Table 4.1 Age and parity of women attending the IBS service according to whether their symptoms fulfilled Rome III criteria for irritable bowel syndrome (IBS), another functional gastrointestinal disorder (FGID) or none

	ROME III positive		ROME III negative	P-value
	IBS	Other FGID[a]		
Number	187 (74%)	28 (12%)	16 (7%)	
Median age (range) in years	**37 (13-84)**	**47(20-84)**	**46 (17-79)**	**0.02[b]**
Nulliparous	97 (50%)	10(35%)	6 (37%)	0.17[c]
One child	**12 (6%)**	**3 (10%)**	**0 (100%)**	**<0.0001**
Two children	46 (24%)	11 (38%)	5 (31%)	0.24
Three or more children	32 (17%)	4(13%)	5 (31%)	0.15
Endometriosis	**59 (31%)**	**2 (7%)**	**3 (18%)**	**0.01**
Rectocele	59 (31%)	6 (21%)	3 (18%)	0.34

[a] functional bloating n=21; functional diarrhoea n=4; functional constipation n=3

[b]One way Anova

[c]Chi-square test

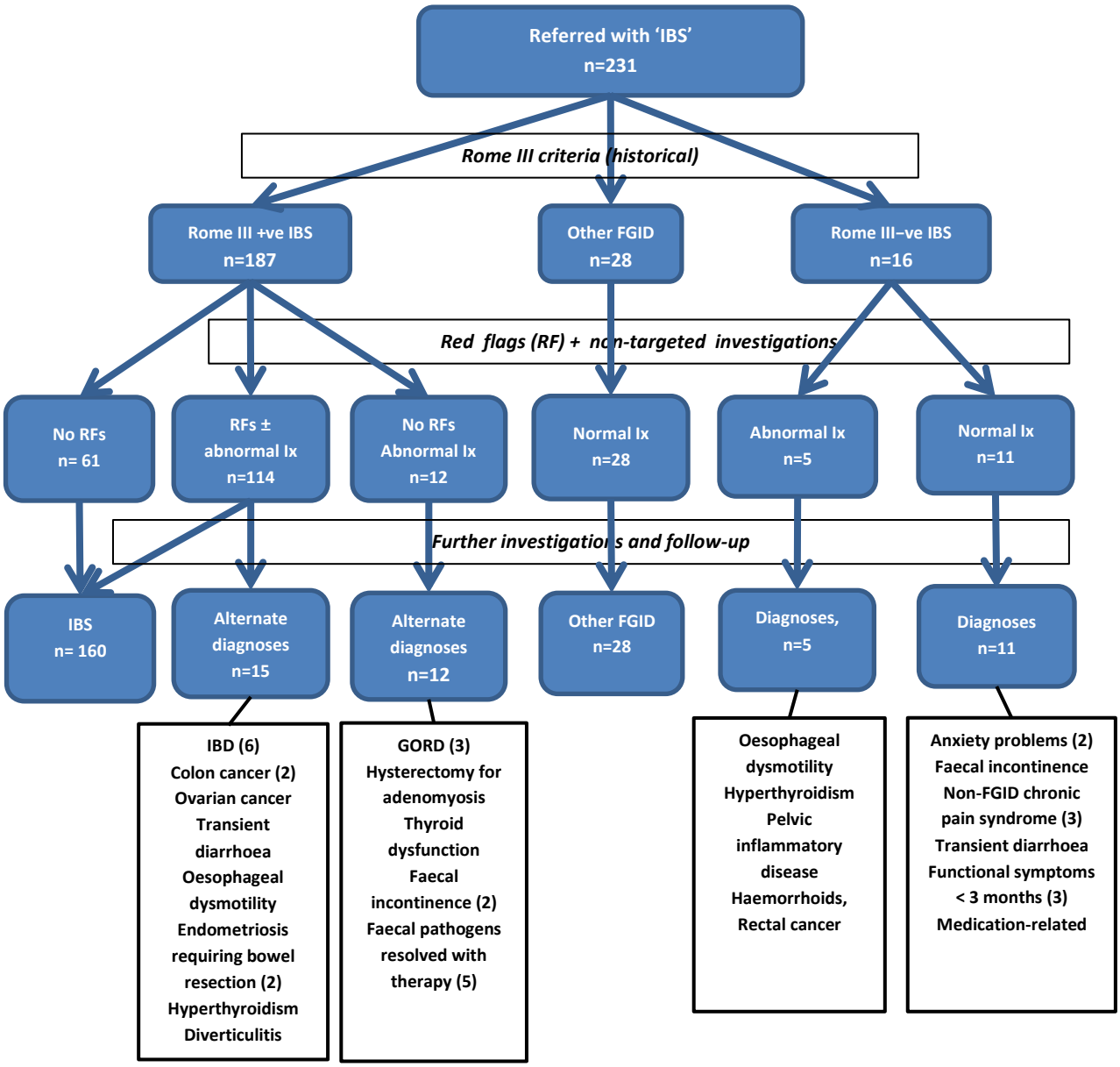

Figure 4.2 Stratification of patients attending the IBS service and progressive disposition

4.3.2 Contribution of red flags and laboratory tests to the diagnosis

The red flags reported by women initially meeting Rome III criteria for IBS are shown in Table 4.2. The number of red flags identified was predictive of organic disease with three or more associated with an alternate diagnosis although the presence of only one red flag was associated with a final diagnosis of IBS (Table 4.2). Of the laboratory tests, faecal calprotectin was the most frequently abnormal. In

those in whom the faecal calprotectin was >500 μg/g, all (n=8) had inflammatory bowel disease or colorectal cancer. Of the others, most had normal gastrointestinal investigations that included colonoscopy.

Table 4.2 The frequency of red flags used in the questionnaire in relation to the final diagnosis in those initially meeting Rome III criteria

	IBS N=160	**Alternate diagnosis N=27**	**P-value** Fisher's exact test
Weight loss >5 kg over last 6 months	14 (8%)	5 (18%)	0.16
Rectal bleeding	49 (30%)	7 (25%)	0.82
Melaena	14 (8%)	5 (18%)	0.16
Nocturnal bowel symptoms	52 (32%)	11 (40%)	0.50
Age >50 years	37 (23%)	12 (44%)	**0.03**
Family history of colorectal cancer or inflammatory bowel disease	42 (26%)	8 (%)	0.8
Faecal calprotectin >100 μg/g	4 (2%)	10 (37%)	**<0.0001**
Faecal calprotectin > 500 μg/g	0	8 (29%)	**<0.0001**
Number of red flags: Any	98 (61%)	15 (55%)	0.67
1	70 (43%)	2 (7%)	**0.0002**
2	22 (13%)	4 (14%)	1.00
≥ 3	6 (3%)	9 (33%)	**<0.0001**

Alternative diagnoses in patients with red flags or abnormal investigations are shown in Figure 4.2. Of those in whom laboratory investigations were abnormal in the absence of red flags, six directly led to the diagnosis (thyroid dysfunction in one and intestinal infection in five, all responding to appropriate treatment), while in the other six, the abnormal tests were not directly relevant to the underlying diagnosis (gastro-oesophageal reflux disease in three, adenomyosis requiring hysterectomy in one and faecal incontinence in two).

4.3.3 Clues to pelvic floor dysfunction

The prevalence of rectocele on rectal physical examination was 31% with no significant difference between those with and without IBS (Table 4.1). Table 4.3 shows the demographics and symptoms in relation to the presence or absence of a rectocele. Symptoms associated with pelvic floor dysfunction were identified as: straining more than 70% of the time, a sense of incomplete evacuation more than 70% of the time, and digitation or splinting to assist in defaecation. There was no significant difference in age, but the symptoms reported did differ between those with or without rectocele. Constipation as their main stool type was about four times more common in patients with a rectocele, and diarrhoea predominance more than one-third less common. Lower abdominal pain was one fifth as likely to be reported in those with rectocele.

Table 4.3 Demographics and presenting symptoms of patients with rectocele. Age analysed via unpaired t-test; parity and symptoms analysed via Fisher's exact test. Statistical significance was set at 0.004 when adjusted via Bonferroni correction

	Rectocele		P value	Odds Ratio (95% CI)
	Present n=59	**Absent** n=101		
Median age (range)	38 (16-81)	33 (13-84)	0.33	-
Nulliparous	24 (40%)	64 (63%)	**0.008**	**0.39 (0.20-0.76)**
One child	2 (3%)	10 (10%)	0.21	0.31 (0.06-1.51)
Two children	19 (34%)	24 (23%)	0.14	1.72 (0.84-3.49)
Three children	9 (14%)	11 (10%)	0.46	1.47 (0.57-3.79)
Four or more children	3 (5%)	3 (3%)	0.67	1.75 (0.34-8.9)
Dyspareunia	15 (25%)	25 (24%)	1.00	1.03 (0.49-2.17)
Menses affect symptoms	37 (62%)	60 (59%)	0.73	1.14 (0.59 -2.22)
Pain referred to back or pelvis	47 (79%)	80 (79%)	1.00	1.02 (0.46- 2.27)
Mid-cycle pain	5 (8%)	13 (12.8%)	0.44	0.62 (0.21-1.85)
Nocturnal symptoms	17 (30%)	35 (30%)	0.48	0.76 (0.38-1.53)
Low abdominal pain	41 (72%)	93 (92%)	**0.0003**	**0.19 (0.07-0.48)**
Better after bowel motion and passage of flatus	32 (59%)	56 (55%)	1.00	0.95 (0.49-1.81)
Strain >70 % time	28 (49%)	26 (25%)	**0.005**	**2.60 (1.32-5.13)**
Urgency >70% time	10 (17%)	32 (31%)	0.04	0.44 (0.19-0.97)
Sense of incomplete evacuation <70% time	38 (66%)	37 (36%)	**0.0002**	**3.61(1.86-7.02)**
Food main trigger	30 (52%)	57 (56%)	0.51	0.79(0.41-1.52)
Eating out triggers symptoms	14 (24%)	30 (29%)	0.46	0.76 (0.35-1.53)
Endometriosis	17 (30%)	39 (38%)	0.23	0.64 (0.32-1.28)
Digitation or splinting	21 (36%)	7 (6.9%)	**<0.0001**	**7.42 (2.91-18.90)**

4.3.4 Presence of endometriosis

The overall prevalence of endometriosis was 27%. Patients who had IBS were significantly more likely than those without to be diagnosed with or have a past history of endometriosis (31% vs. 11%; P=0.007). In the patients with a final outcome of IBS (n=160), analysis of symptoms and demographics indicated age, nulliparity, family history of endometriosis, dyspareunia, menses affecting bowel symptoms and pain referred to the back and pelvis were associated with the presence of endometriosis (Table 4.4).

4.3.4.1 Response to the low FODMAP diet

Adherence to the diet was high in both groups with only four (7%) in the endometriosis group and ten (9%) of IBS-alone group not adhering to the diet sufficiently to assess efficacy. Overall, the diet was reported as being effective (>50% improvement in symptoms) by 92 (58%) women meeting Rome III criteria for IBS. (Table 4.5) A significantly higher proportion of patients with known endometriosis responded to the diet (n = 43, 72%) compared with those without (n = 49, 49%; p=0.001) according to intention-to-treat. This represented a threefold increase in the likelihood of responding to the low FODMAP diet compared to those without endometriosis (Table 4.5).

Table 4.4 Demographics and presenting symptoms of patients with endometriosis. Age was analysed via unpaired t-test; parity and symptoms analysed via Fisher's exact test. The statistical significance was set at ≤0.003 with the Bonferroni correction

	Endometriosis		P-value	Odds Ratio (95% CI)
	Diagnosed n=59	Not diagnosed n=101		
Median age (range) years	28 (16-65)	38 (13-84)	**0.006**	-
Nulliparous	40 (67%)	51 (50%)	**0.04**	2.06 (1.05-4.03)
One child	4 (7%)	8 (7%)	1.00	0.84 (0.24-2.93)
Two children	12 (20%)	31 (30%)	0.56	0.77 (0.35-1.69)
Three children	3 (5%)	17 (16%)	0.07	0.30 (0.08-1.11)
Four or more children	0	6 (5.3%)	0.08	0.12 (0.00-2.23)
Family history of endometriosis	11 (18%)	2 (1.9%)	**0.0003**	11.34 (2.41-53.2)
Dyspareunia	29 (50%)	13 (12%)	**<0.0001**	6.54 (3.01-14.2)
Menses affecting bowel symptoms	45 (75%)	54(53%)	**0.004**	2.79 (1.36-5.72)
Pain referred into pelvis and back	53 (89%)	66 (65%)	**0.0006**	4.6 (1.83-11.9)
Mid-cycle pain	11 (19%)	7 (6%)	**0.02**	3.42 (1.26-9.28)
Nocturnal symptoms	28 (46%)	27 (26%)	**0.009**	2.47 (1.2-4.8)
Low abdominal pain	56 (94%)	90 (89%)	0.25	2.28 (0.60-8.53)
Relief after a bowel motion or passage of flatus	34 (58%)	64 (63%)	0.5	0.78 (0.40-1.51)
Straining >70% time	22 (37%)	36 (35%)	0.28	1.47 (0.73-2.94)
Sense of incomplete evacuation >70% time	26 (44%)	59 (58%)	0.10	0.57 (0.30-1.09)
Urgency >70% time	9 (15%)	36 (35%)	**0.006**	0.32 (0.14-0.73)
Food main trigger of symptoms	34 (58%)	66 (65%)	0.39	0.72 (0.37-1.39)
Eating out triggers symptoms	22 (33%)	29 (28%)	0.29	1.47 (0.74-2.91)
Rectocele	17 (29%)	33 (32%)	0.7	0.83 (0.41-1.68
Digitation or splinting	9 (15%)	19 (18%)	0.66	0.77 (0.32-1.85)

Table 4.5 Adherence and response to the low FODMAP diet in patients with irritable bowel syndrome with or without concomitant endometriosis. Adherence was defined as those who persisted with the diet for 4 weeks. Response was defined as a greater than 50% improvement in symptoms

	Endometriosis N=59	**No reported endometriosis N=101**	**P value** Fisher's exact test	**Odds ratio (95% CI)**
Adherence to low FODMAP diet	55 (93%)	91 (90%)	0.57	1.5 (0.45-5.05)
Success with Low FODMAP Diet	43 (72%)	49 (49%)	**0.001**	**3.11 (1.5-6.2)**

4.4 Discussion

4.4.1 History taking, physical examination, red flags and investigations

In this study, a nurse-led protocol sequentially evaluated patients via historical information, a pertinent physical examination followed by evaluation of clinical red flags and then simple, limited routine laboratory testing. Via this method, of those initially fulfilling IBS criteria 13% with red flags, and 6% without red flags were found with alternate diagnoses that successfully guided management away from IBS paradigms. It has been recommended that a positive diagnosis is made based on symptom criteria, such as those developed by the Rome Foundation[25, 206] with subseqeunt investigation according to the presence of red flags. While symptoms of IBS that fulfil Rome III criteria are a good guide to the final diagnosis of IBS, alternate or concurrent diagnoses can be missed. However, red flags are common as shown in the present study where two out of three patients had at least one of the clinical red flags used in the questionnaire. This frequency was similar to that reported previously[26]. It might then be considered that this approach is rather non-discriminatory. Nevertheless, one in three did not require further investigation. Furthermore, the presence of red flags or abnormal tests does not implicate extensive subsequent investigation. Rather, their presence should lead to greater suspicion and more careful clinical assessment, with more invasive and

expensive investigations such as colonoscopy targeted towards those warranted by clinical suspicion not the presence of red flags alone[40].

The use of a structured protocol for a nurse-led clinic including history taking and physical examination contributed to the identification of alternate diagnoses. For example, the abdominal examination identified an abdominal mass which turned out to be an ovarian tumour, observation and palpation of the thyroid gland identified a unilateral swelling, digital rectal examination identified rectoceles, as well as looking for other pelvic floor abnormalities, lesions, fissures or the presence of blood[39].

Unfortunately, the art of physical examination appears not to be applied optimally in the primary care sector[93], with it being reported that few physicians examine the pelvic floor or perform a digital rectal examination to assess the tone of the external anal sphincter in constipated patients[22]. In this study employing the use of physical examination was integral towards a more accurate diagnosis. Reasons why this art is not always employed include the fact that physical examination can be time consuming, and there is more reliance on the results generated from the application of modern testing equipment[207, 208], where there is a concern that new generations of clinicians are not developing critical physical examination skills.

It has previously been identified that a structured protocol for advanced-practice nurses has better results in patient compliance than some physicians[209]. The keys in using such a protocol in practice are first, that it could standardise the consultation and decision-making process in a group of patients who are frequently time-consuming in busy practices or clinics. The use of an appropriately experienced advanced-practice nurse to identify and manage IBS patients has the advantage of time, validation, and education. An appropriate amount of time needs to be set aside. Applying an appropriate questionnaire and diary ensures no red flags are missed. Secondly, as shown in this study, it should

lead to a confident diagnosis of IBS and a management plan formulated with appropriate reassurance that they are not being dismissed, a frequent complaint among those with functional disorders[46]. Thirdly, this allows more space in the physician's schedule to see people who are better medically managed or requiring more complex strategies. The findings associated with the use of a structured protocol in this study reflect these principles, though the impact on physicians was not examined. A future, prospective study would need to be undertaken, perhaps in the public sector, where there is a different clinical environment.

4.4.2 Relevance of rectocele

Identification of a rectocele was reasonably common in this study (31%) however not as high as identified in the literature where up to 75% women have a rectocele, though many are asymptomatic[210]. This perhaps relates to the fact that only those who were symptomatic were included in this study. Symptoms such as abnormal stool frequency, abnormal stool form, abnormal stool passage such as straining, urgency or feeling of incomplete evacuation, passage of mucus, and bloating or feeling of abdominal distension are often characterised as IBS[30, 73]. However, the findings in this study suggest that straining and incomplete evacuation in particular are more likely related to a rectocele. The need to splint the perineum (apply pressure on the perineum with fingers) in order to pass the stool, or insertion of a finger into the vagina or rectum to assist in emptying the rectum discriminates those with clinically significant rectocele from those without[73, 211] and is of clinical importance in diagnosing pelvic floor dysfunction. This was certainly the case in this study where women with a rectocele were 7 times more likely to need to digitate and 3 times more likely to strain at defaecation.

Taking a good clinical history together with adequate perineal/rectal physical examination are thus important to distinguish a defaecatory disorder from IBS[39, 212]. The more clinical features identified by

a woman increases the chance of pelvic floor dysfunction contributing to IBS symptoms that are likely to require different or additional management strategies. However, if the only classic pelvic floor dysfunction symptom reported was digitation or splinting, in conjunction with detection of laxity of the anterior rectal wall, that should alert the physician to investigate further such as defaecating proctogram or dynamic pelvic floor magnetic resonance imaging[66].

4.4.3 Prevalence of endometriosis

In this study, the prevalence of endometriosis concurrently with IBS was 31% where the symptoms of abdominal bloating, diarrhoea and/or constipation might be attributed to either diagnosis. Difficulties distinguishing between the two conditions are frequently raised as a clinical concern[213]. Because endometriosis is difficult to diagnose[214], defining a symptom profile in patients presenting with otherwise non-specific abdominal symptoms that predict the presence of endometriosis would be valuable. Women with endometriosis in the current study were 13 times more likely to report a family member with the disease than those without endometriosis, consistent with other reports[215]. It is suggested the presence of at least 3 of the following symptoms; dyspareunia, menstruation affecting bowel symptoms, pelvic pain, nocturnal bowel symptoms as well as a family history of endometriosis be included in the list of indices that direct targeted investigation to the presence of endometriosis as these symptoms make endometriosis more likely.

There are two clinically important reasons for the early recognition of the presence of endometriosis in women. First, therapeutic laparoscopy for endometriosis significantly reduces all symptoms, including bowel symptoms, and improved the overall quality of life[213, 216, 217]. Medical management strategies such as oestrogens and progestogens have some benefits for pain, but their side effect profile make them less attractive to some[218]. Secondly, infertility is associated with endometriosis[219] and early intervention reduces the impact of the disease particularly on fertility[219-221]. It is not

surprising that the present study found more women with endometriosis were nulliparous than those without endometriosis (66% vs 46%), although reasons for nulliparity were not explored.

4.4.3.1 The low FODMAP diet for IBS and endometriosis

This is the first study to show a therapeutic benefit of a low FODMAP diet in patients with endometriosis. All patients in this study were taught the low FODMAP diet predominantly for relief of abdominal bloating and pain[115]. This diet has significantly reduced these symptoms in 58% of the total study population. This is in keeping with that of other research findings where responses to the low FODMAP diet in cohorts with IBS have varied from 52 to 80%[113-115, 222].

Interestingly, however, in this study the low FODMAP diet was beneficial in a substantially higher proportion of IBS patients with endometriosis (3 out of 4) than in those in whom such a diagnosis had not been made (1 out of 2). This difference in response rates between those with known endometriosis and those who have not requires explanation. Visceral hypersensitivity has been identified as contributing to bowel symptoms in women with endometriosis[223] and indeed, many women were referred from gynaecologists for help with visceral symptoms. Perhaps endometriosis is a clinical marker of likely visceral hypersensitivity. Since the mechanism of action of the low FODMAP diet is to reduce luminal distension in patients with visceral hypersensitivity, the presence of endometriosis might then be a marker of response to the diet. In fact, the presence of endometriosis is the first clinical predictor of response to the diet identified. There are few studies that explore diet and endometriosis. It has been suggested that a high dairy intake and vitamin D may have some preventive effect,[224] but no studies have looked at diet having a therapeutic effect. Further research, ideally a prospective randomised controlled trial exploring the efficacy of the low FODMAP diet in endometriosis, is needed. At the least, a prospective pilot study is warranted to confirm the findings of this study.

4.4.4 Limitations

The current study had several limitations inherent in a single-centre, retrospective analysis. However, the diary data were collected prospectively. Selection bias may have been present as patients attended a private clinic, which would skew the socioeconomic characteristics of the population and potentially limit the generalizability of the findings. The sensitivity of examination for rectocele may be questioned, but assessment was independent of the questionnaire, and its presence was strongly associated with symptoms of straining to pass a stool, digitation to assist defaecation and a sense of incomplete evacuation. The characterisation of the patient cohort with respect to endometriosis depended upon an established diagnosis. Not all women had a laparoscopy and it was assumed that those who did not had a low chance of endometriosis. The intervention was not placebo-controlled, but this does not detract from the sub-group analysis where it might be predicted that placebo responses were roughly similar. Unfortunately, a validated tool was not used to assess the response to the diet but rather a global assessment made by the clinician. Furthermore, changes in individual symptoms were not used, although previous studies have uniformly shown improvement of all IBS symptoms associated with the diet.

4.5 Conclusion

In conclusion, relying on identification criteria for IBS alone without pertinent investigations of red flags may mean alternate or concurrent diagnoses are not detected. An appropriately experienced nurse using a structured protocol that include clinical tools of history taking and clinical examination can contribute toward a higher chance of a confident diagnosis of both IBS and/or an alternate problem. This is in conjunction with simple laboratory investigations where abnormalities and/or red flags lead to additional appropriate investigations. Appropriate management strategies or referral on

are subsequently instituted. Of potential importance in women are the symptoms of co-existing pelvic floor dysfunction. While such symptoms have often been associated with IBS, their presence may prompt different and specific investigative and therapeutic strategies. Endometriosis appears common in women with IBS. Historical clues identified included dyspareunia, low pelvic pain and a family history of endometriosis, and these should lead to investigation and treatment that may assist in reducing complications from endometriosis such as infertility. The low FODMAP diet is beneficial in reducing bowel symptoms in women with endometriosis. Indeed, the presence of endometriosis may be a clinical predictor of a higher likelihood of response to the low FODMAP diet, presumably because of the causal association with visceral hypersensitivity.

This chapter included the role of a protocol used by a nurse in identification of alternate diagnoses to IBS and concurrent comorbidities. One of these comorbidities was found to have a novel management strategy. Using a protocol ensured safe practice. The next chapter explores another role nurses have in preventing the development of constipation in hospitalised patients via the use of a protocol that was developed as an evidence based care plan. This care plan has management strategies that require little medical input and empowers nurses to make decisions in managing their patients' bowels.

CHAPTER 5: EVIDENCE-BASED, NURSE-LED MANAGEMENT OF CONSTIPATION IN THE HOSPITALISED PATIENT

5.1 Background and aims:

Constipation is a common, preventable problem among hospital inpatients. This is particularly troublesome in patients with acquired brain injuries who are recovering in a specialised rehabilitation setting[225]. Constipation occurs in up to 60% of patients in early weeks following a brain injury, though approximately 30% still experience difficulties at 36 weeks post injury[191]. Alterations to gut motility commonly occur following brain injury. Depending on the location of the injury in the brain, intestinal peristaltic actions and sequences associated with defaecation can be impaired, as can rectal sensation potentially leading to faecal impaction[225]. Overflow incontinence, as discussed in Chapter 1, frequently develops as stool above the impaction is generally liquefied[85], seeping around the impacted stool. The prevalence of faecal incontinence associated with constipation in those recovering from brain injury is up to 40%, though this rate does drop with time from the injury[225]. Persistent incontinence with a traumatic brain injury may be associated with a poorer functional outcome[87], where those with bowel dysfunction incur higher costs, and are far more likely to be placed in a nursing home rather than their home of choice[226].

In addition to degrees of immobility, these patients are more likely to be on medications commonly contributing to constipation[227]. The inability to communicate and a lack of awareness of social mores associated with a brain injury compound this[225]. Clinical staff attitudes also impact on how constipation or faecal incontinence is managed; it has been identified that management of bowel

activity is of low priority in the critically ill, not believed to be a major problem[228]. Because constipation is not seen as a life-threatening situation, often not even viewed as a complication, it is a much neglected study subject with a lack of high quality studies[191].

In both the intensive care unit (ICU) setting and rehabilitation, there have been studies on the use of bowel management protocols to improve patient outcomes[228], but there is a general paucity of information in this area. Barriers to implementation stretch across all members of the clinical management team. These include knowledge, beliefs, behaviours and attitudes of clinicians and nurses, and assessment tools used such as how bowel function is assessed and the use (or lack) of digital rectal examination[228]. Maintaining an accurate record of bowel function is a further barrier[229] especially in these times of change in reducing use of paper instead using electronic means of observing and recording.

The current practice observed in the Acquired Brain Injury Unit (ABIU) is that patients at risk of developing constipation are prescribed regular laxatives, on an ad hoc basis, by medical staff. All too frequently some of these patients have loose bowel motions daily and are incontinent. There is an absence of information on evidence-based regular laxative use in hospitalised patients[230]. It has been suggested that there is less risk of incontinence in long-term care if laxatives are used on an as-needed basis[231] allowing the bowel a chance to regain function independently.

There is a varied experience of the effectiveness of education and implementation of bowel management protocols. In the ICU setting, gradual but significant improvement in documentation was observed in one study[189] and improved patient outcomes irrespective of whether nurse- or physician-led in another[209]. Translation of complex protocols to a brain-injury rehabilitation setting where input and interaction with patients is not always possible[226]. Finding a protocol to suit is difficult, where

some appear confusing and not pertinent[189]. A successful protocol needs to be specific, easy to follow and easy to apply, and allows the individual patient's bowels a chance to function independently where potentially the ability to regain continence is achievable. It also needs to be prescriptive, empowering nurses to make safe decisions according to best practice, and based on clinical evidence[66, 119, 190-192].

Therefore, the aims of this study are (1) to implement a novel nurse-led evidence-based bowel management plan suitable for use in the ABIU*;* (2) to identify impediments to appropriate management of constipation in the ABI; and (3) to evaluate its impact on staff behaviour around administration of laxatives, documentation and attitudes. It was hypothesised that nurses would find this an effective means of managing patients at risk of constipation and improve their knowledge levels, confidence and documentation behaviours accordingly.

5.2 Ethics

The project was approved by Alfred Ethics in July 2016 with the study number 300/16.

5.3 Methods

A 3-phase study was performed as outlined in Table 5.1.

5.3.1 Setting and participants

This research project was conducted at the ABIU in Caulfield General Hospital in Melbourne. This is a 42-bed specialised rehabilitation unit for patients with an acquired brain injury. The source of patient bowel data was electronic bowel charts from the ABIU assessing documentation of the patient's bowel activity, stool type, and incidence of laxatives given, as shown in Figure 5.1. Information on prescribed

medication was accessed from patient drug charts in the unit and documentation in nursing notes. Nurses were the study participants who completed questionnaires and participated in a focus group session.

Table 5.1 Outline of the study method for nurse-led management of constipation in the hospitalised patient

Study phase	**Research activity**
Phase 1	Baseline audit of 3 month's data from electronic bowel charts. Pre-implementation questionnaire to nurses. Focus group session.
Phase 1b	Development of a protocol on the use of Movicol with thickened fluids
Phase 2	Education session on care plan and electronic bowel diary documentation. Implementation of the evidence based care plan.
Phase 3	Audit of bowel charts three months after implementation. Post-implementation questionnaire to nurses.

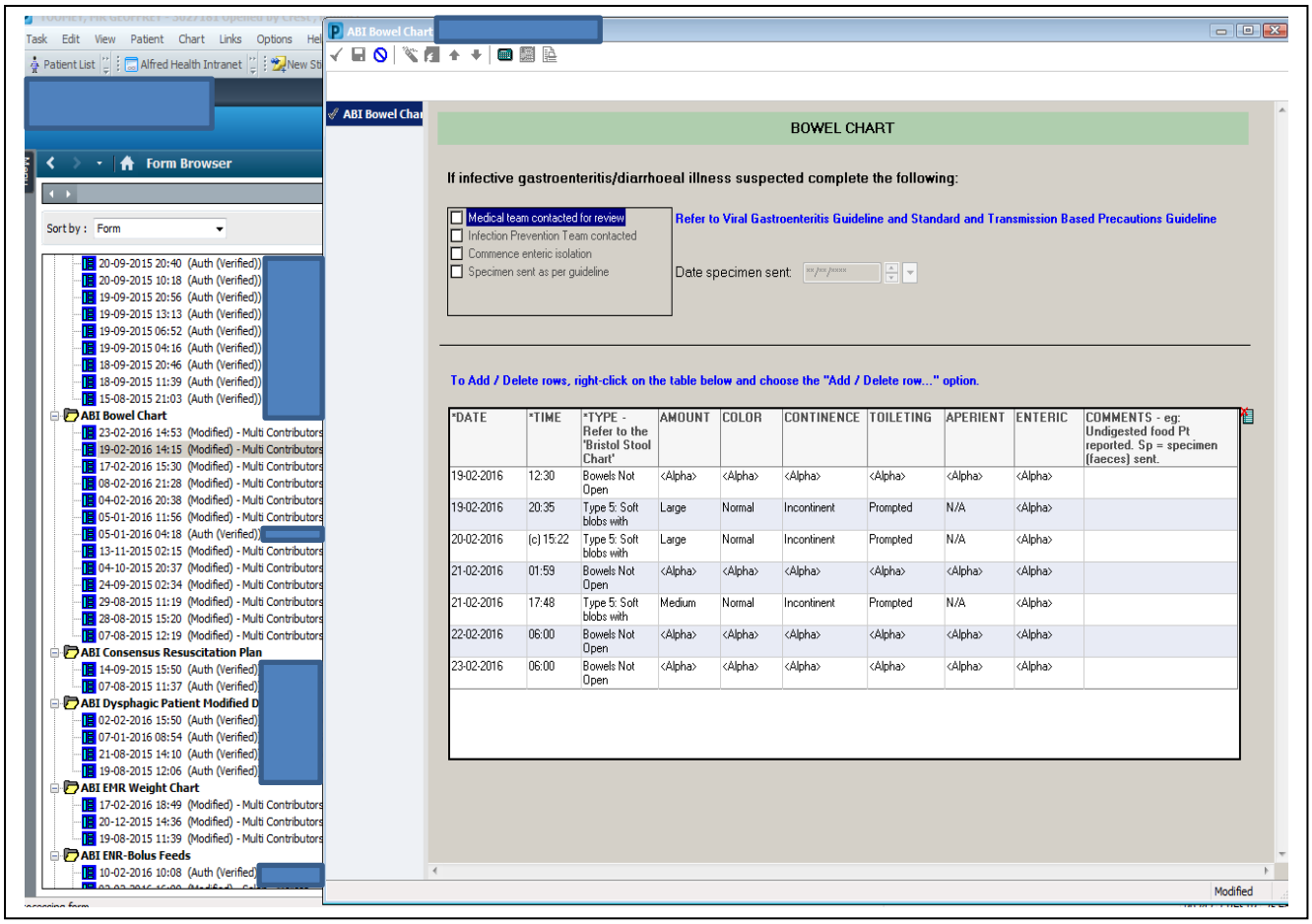

Figure 5.1 An example of the electronic bowel chart as used in the ABIU

5.3.2 .Evidence based bowel care plan

An evidence-based bowel care plan was created (see Chapter 3.4.1.1) for use by nurses in the ABIU. This was implemented after education sessions for nurses on this plan had been conducted combined with reinforcement of appropriate documentation in the electronic bowel charts.

5.3.3 .Electronic bowel chart data

Three months' worth of retrospective data from the electronic bowel charts was collected before education and implementation of the evidence-based bowel care plan. The electronic bowel charts were examined again at 3 months following implementation of the care plan.

5.3.4 .Questionnaires

Nurses were given a brief questionnaire to complete before the introduction of the intervention. A description of this questionnaire is in Chapter 3. The same questionnaire was given to the same nurses 3 months after implementation of the evidence-based bowel care plan. A change in VAS scores of 10 mm or greater were arbitrarily considered clinically significant.

5.3.5 .Focus Group

A focus group session was held to identify potential problems and to help determine the more strategic approach without adding to the nurses' busy workload. This was deemed the most appropriate method of gaining insight into the thoughts and problems around constipation in an efficient and timely manner. One session was held for nurses expressing an interest in participating. This session ran for 45 minutes with questions that were centred around a definition of constipation, perceptions of how much of an issue it was on the ward, what the current policies and practices were when someone was found to be constipated and what impediments there were to managing constipation on the ward. The final question asked how can we better manage it. Data from the focus group was obtained via the use of an electronic recording of the session that was then transcribed. Themes were extracted, the transcript having been read by 2 other researchers with whom discussion around the emerging themes was had.

5.3.6 .Development of a regimen for institution of PEG-containing laxatives in patients with dysphagia

There was the potential for some patients in the ABIU to have dysphagia and would only able to drink fluids that are thickened to reduce the risk of aspiration. Consequently, a protocol on the use of an iso-osmotic laxative based on macrogol (Movicol, Norgine Australia, Frenchs Forest, NSW) with thickened fluids that are preferred for use at the ABIU was developed in conjunction with the senior speech pathologist should the need arise. The creation of this protocol is outlined in Chapter 3.

5.3.6.1 Education

Education sessions were held to address the identified impediments and to introduce the bowel care plan for all staff following which the evidence-based care plan was then charted in the patients' notes. Further one-on-one sessions were held for nurses who could not attend the main sessions.

Once the focus group session had been undertaken, questionnaires completed and education sessions had occurred, the care plan was documented in the patients' charts by the resident medical officer except for those patients for whom the plan would not be relevant, such as in patients with an ileostomy. Nurses were now directed by the ward nurse educator to monitor bowels each shift where accurate documentation in the electronic bowel chart was reinforced, and to refer to the care plan instead of contacting the doctor if bowels not open.

5.3.6.2 Outcome measures

The primary endpoints for this study were the documentation of laxatives in the electronic bowel chart, the incidence of PRN laxatives used and the incidence of regular laxatives charted. Other

outcome measures include the change in responses in the nurses' questionnaires and the incidence of bowels not open (BNO) recorded in the electronic bowel chart.

5.3.6.3 Data analysis

Fisher's exact test was employed to determine the difference in documentation of laxatives between the pre-implementation of the care plan and following its use for 3 months. A paired t-test was used for analysis of change in VAS scores.

5.4 Results.

5.4.1 Focus group session.

The focus group comprised 6 nurses, the nurse educator who made notes on the discussion, and the interviewer who recorded the conversation for analysis. Consistent themes emerged on challenges identified in managing and documenting bowel activity in focus group and these are summarised in Table 5.2.

The nurses' definitions of constipation ranged from *"having a hard tummy"* to *"hard stools"* and "*discomfort, haven't been for several days"*. The nurses generally perceived that constipation was not a big problem in the ward, and that the bedridden patients, particularly those on PEG feeds, were more likely to have diarrhoea with faecal incontinence was the main issue. They felt that, when people were constipated, it was frequently missed. Comments included: *"it's common that it's missed", "constipation is not common, but when it does happen it's missed"* and *"this is an area we need to improve on"*. Current practice on the ward when someone was found to be constipated was to check if an aperient was charted and, if not, the doctor was contacted to prescribe a laxative. Themes identified revolved around time, remembering or forgetting to document bowel activity, and the

electronic bowel charts, which were not popular. It was identified that they should be checking the bowel charts regularly, but this was not always happening. It was sometimes brought to their attention by the doctor who was checking the bowel charts. Impediments to monitoring patient's bowel activity were a combination of problems, the biggest issue being the use of the electronic bowel charts themselves. To monitor and document bowel activity meant leaving the bedside and going to the nurses' station to both check and record, as it was during the drug rounds that was the ideal time to note if intervention was needed. Comments included *"We have to go to the office. It's just so busy like … you have to go back to check a bowel chart – you're just not going to do it"*. As a result, it was frequently missed, with the nurse forgetting to check or annotate when they were finally in the office. Bowel activity was often documented in the nursing notes, but an additional action to enter the information in the electronic chart was needed. Another impediment was the reliability of information of cognitively-impaired ambulatory, self-toileting patients who could not be relied upon to give a true answer when asked if their bowels had moved. Again, the time factor arose with several discussing the fact that they cannot stand over and watch the patients. For example, a typical response was *"The only time it worked was with a patient who had an alarm mat every time he got up, so the staff were frequently with him when he went. Unfortunately, this practice was only followed for a week"*.

There was enthusiasm around the question of how they do it better. A common theme was the need for something in the bedroom or on the door that was a prompt for them, such as something they could tick, or a visual reminder to both ask and to document. They felt that such prompts would be associated with a greater likelihood to document in the bowel chart at the end of the shift. Suggestions were made as to how one particular shift was responsible for ensuring bowel activity had been noted; there was unanimous agreement that night staff were more likely to have time to do this, and they could hand over to the morning staff on each person's bowel status. It was also suggested that there was a protocol in the front of each patient's chart they could follow if bowels had not

opened; examples of responses included *"would like a plan in front of the chart to say what to give"* and *"something that says what to give on, say 2nd day of bowels not open give this, 3rd day give that"*.

Table 5.2 Themes emerging from the focus group on challenges identified in managing and documenting bowel activity in focus group

• Not enough time to go to the office to document in electronic bowel chart
• Forget to document as they cannot do it at the time
• Cognitively impaired patients who self-toilet won't remember stool type or if bowels had opened
• Bowel charts are an impediment, not useful. Already document in patient notes and on drug chart
• Too busy. Need a better way of flagging when someone is constipated

5.4.2 Movicol and thickened fluids for dysphagic patients.

The use of starch thickeners was found to paradoxically render the Movicol as a runny consistency. The use of xantham gum (E415) as a thickener proved to be reliable in maintaining thickness when combined with the macrogol. Thus, xantham-gum-thickened fluids (Flavour Creations Pty Ltd, Acacia Ridge, Queensland) were provided in the ward in ready-made containers of 185 ml in 3 different thicknesses and 2 different flavours, as well as plain thickened water. Sachets of Movicol were successfully mixed with all 3 consistencies and flavours to the recommended volume of 125 ml. (Chapter 3). The Movicol and thickened fluid policy (Chapter 3, Table 3.3) was adopted and made available in the ABIU for use.

5.4.3 Audit of electronic bowel charts before the intervention.

Twenty-two patient charts, each spanning a 90-day period, were examined before the intervention. According to review of nursing and medical notes and of drug charts, all 22 patients were identified as at-risk for constipation due to prescription of either opiates, antipsychotic agents or both. According to the drug charts all but 6 patients had regular laxatives documented, mostly Coloxyl and Senna. Two patients were prescribed as-needed (PRN) laxatives only. Four did not have any laxative charted.

All 22 patient charts had multiple electronic bowel charts (Figure 5.1) each one needing to be opened to identify bowel activity. Seventeen patients had their stool type reported as being Bristol stool type 5, 6 or 7 most of the time. Only 5 patients had any laxative use documented in the electronic bowel chart. One of the 5 of these had charted *"patient report BNO [bowels not opened], aperient given as charted"* on one occasion only, but this particular patient frequently had several consecutive days of BNO noted, the longest period being for 5 consecutive days. Two charts had PRN medication recorded on one occasion only, 1 chart had PRN medication recorded on 3 occasions when BNO for more than 3 days. One chart recorded suppositories on 39 occasions. One patient had a Bristol stool scale 6 ooze reported after BNO for 3 days, but no action recorded. Another 2 had BSS type 7 after BNO for more than 3 days on one occasion and after 4 days on another, but no action was noted. Nine patients had 3 or more days in a row of BNO, one being 7 days in a row where it was noted in the nursing notes on admission that there was faecal loading. Again, no action was recorded in the electronic bowel chart.

Following 3 months' implementation of the evidence-based bowel care plan, nurses reported finding the tool useful, appreciative of the fact that they could implement an action without needing to consult medical staff. Twenty-two electronic bowel charts were audited examining the previous month's recorded data. A comparison of the key data are shown in Table 5.4. Documentation of

laxatives in the electronic bowel chart significantly improved following education with the care-plan though it was erratic. There were also fewer new electronic bowel charts created, but it was reported that with time constraints it was much quicker to create a new one than wait for an existing one to open.

Table 5.3 Comparisons of data obtained from the electronic (E) bowel chart and drug chart before and after 3 months' implementation of the evidence-based bowel care plan

Outcome	**Pre-intervention N=22**	**Post-intervention N=22**	**P value** Fisher's exact test
Number of patients (%) with BNO[a] > 2 days	11 (50%)	12 (54%)	>0.99
No of E charts with regular laxatives documented	1 (4%)	13 (59%)	0.0002
No of E charts with PRN[b] laxatives documented	4 (18%)	9 (41%)	0.18
Drug charts with regular laxatives	18 (82%)	13 (59%)	0.18
Drug charts with PRN laxatives documented	2 (9%)	16 (72%)	<0.0001

[a] bowels not opened

[b] as-required

5.4.4 Responses from the nurse questionnaires

The questionnaire pre-implementation was completed by 24 nurses, of whom 14 completed the same questionnaire after 3 months of implementation of the bowel care plan. Ten nurses were no longer working in the ABIU.

Pre intervention, 21 nurses (88%) felt that enquiry about bowel activity from patients should occur every shift and 3 felt daily was sufficient. Post-intervention, 13 of 14 felt bowel activity needed to be checked every shift, and one felt it needed to be daily (Table 5.4).

In comparing VAS scores in the nurses' questionnaires, 3 of 14 nurses increased their score by more than 20mm on knowledge of the Bristol Stool scale. Three felt constipation impacted more on their workload after implementation of the care plan, where 2 felt it impacted less; 3 felt constipation impacted more on the patient than they had previously thought where 2 felt it to be less of an issue. There was a significant change in scores for an increased confidence level in managing constipation after implementation of the care plan, though only 4 had a change of more than 20 mm. Four had a change of 15 mm and 2 by 10 mm (arbitrarily considered of clinical significance – see Methods).

Table 5.4 Comparison of the impressions and beliefs as obtained from the responses on the 100-mm visual analogue scale (VAS) shown as mean (range) to 4 questions asked of 14 nurses prior to and following 3-months' implementation of the care plan

Question	Pre implementation N=14 Mean (range)	Post implementation N=14 Mean (range)	P value *Paired t test
Knowledge of Bristol Stool Scale	91 (70 – 100)	94 (75-100)	*P= 0.43 ns
Impact on work load	54 (25 – 90)	58 (20-90)	*P=0.65 ns
Constipation impact on patients	79 (55 – 95)	90 (65-95)	*P=0.77 ns
Confidence in managing constipation	79 (45 – 90)	85 (60-100)	***P=0.001**

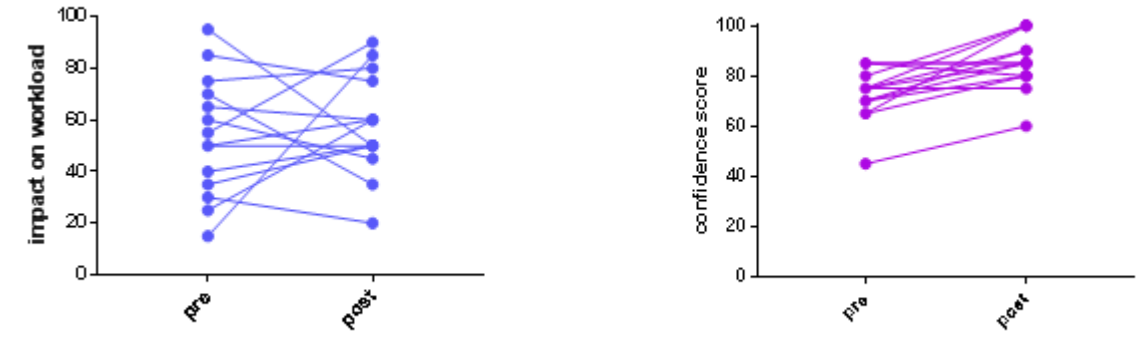

Figure 5.2 The effects of implementation of the care plan after 3 months on A: the nurses' perceptions of impact of patient constipation on their workload; and B: the nurses' level of confidence in managing patient bowel symptoms

5.5 Discussion

Figure 5.2 The effects of implementation of the care plan after 3 months on A: the nurses' perceptions of impact of patient constipation on their workload; and B: the nurses' level of confidence in managing patient bowel symptoms

The effects of nurse-education and implementation of an evidence-based and practical bowel care plan on management behaviours around constipation in patients in the ABIU were evaluated in the present study. A prior audit of the electronic bowel charts had found they had not been utilised as they were intended and indeed, the nurses found them time-consuming. (Table 5.2) The pre-implementation audit of these charts identified information on laxative use in only 1 of 22 charts, and it was not possible to gather accurate information from them. Despite reasonable self-confidence in their knowledge and ability to manage constipation in patients in the ABIU, the institution of the program led to better documentation, greater knowledge and more self confidence in making nursing decisions. It appeared to also be well accepted by medical staff regarding bowel management, doctors

opting to reduce use of regular laxatives from 82% to 59% of patients; concomitantly, PRN management increased from 9% to 72% (P=<0.0001). Use of the electronic bowel chart was still sub-optimal, but some small gains were shown in documentation of laxative use where 13 of 22 charts had intermittent recording of laxatives after education as opposed to 1 chart prior.

The improvement in documentation of laxatives in the electronic bowel charts (Table 5.4) was likely the result of dedicated reminders by one of the senior nurses who assisted in this study. There appeared to be a pattern to intermittent documentation, possibly where nurses may have been reminded. A higher physical presence by the researcher may have provided more positive reinforcement with better compliance. Erratic documentation of bowel management is not unknown, where one study achieved a 13% improvement in documentation after implementing a bowel management protocol[189] noting nurses needed routine prompting. However, the current prospective study does demonstrate that introduction of a structured plan brought bowel management to the fore, and the positive involvement by nurses and their increased confidence likely contributed to a change. This finding has been reflected in studies also introducing a bowel management plan for nurses both in the ICU setting and rehabilitation[189, 229], though there was more resistance to change in the rehabilitation unit[229]. Prior to education and introduction of the evidence-based care plan there was the general perception that constipation was not a problem in the ward – as evidenced by discussion in the focus group and the nurse questionnaire. This perception is not uncommon, there are frequent comments in the literature around the lack of interest in constipation as a problem in hospital, as it is not deemed life-threatening[191, 229]. However, there is increasing recognition, particularly regarding those in long-term management facilities, that constipation in hospitalised patients is a significant health concern. Nevertheless, there is still a paucity of studies on how to best this concern[226]. While nurses are in the best position to manage bowel activity, many still lack confidence in making an autonomous decision[232]. It has been shown that specific education sessions

to nurses on bowel management and active involvement improves both confidence and knowledge as well as improving patient outcomes[189, 226]. It is important that nurses have the ability to detect and interpret signs or clues from patients and apply critical thinking for clinical competence[232]. The use of the bowel care plan has prompted more clinical reasoning and critical questioning. This was demonstrated where nurses had created their own handover flowchart to ensure seamless use of the bowel care plan, however these handover charts were discarded after use. The fact that nurses devised their own system suggests an increased awareness of issues with constipation and a desire to work with the bowel care plan. It was anecdotally reported nurses liked the plan and found it easy to use as manifested by the increase in confidence in managing patients' bowels (Figure 5.4). Use of the care plan was evident in the nursing notes and signed for in the drug charts. It was inconsistently documented in the electronic bowel chart.

Time is a major constraint for nurses as was identified in the focus group session (Table 5.2). Frequently, there were delays encountered attempting to open an electronic bowel chart. It was much quicker to create a new bowel chart than to wait for the current one to open. According to the nurse educator there was meant to be only one chart created for each patient on which a nurse each shift would record accordingly. All too frequently there would be many different charts created in the one patient's notes which made examining charts for trends such as frequency of BNO days difficult. As shown in Figure 5.1, there were 13 electronic bowel charts recorded under the heading "ABI Bowel Chart". In some instances, missing days from one chart are in another chart, and it is time consuming scrolling through all charts searching for data. This was addressed in the education sessions where nurses were shown the steps to take and how and what to document under the appropriate pull down menu.

The bowel charts themselves do not appear to be well designed for use in an Australian system, as exemplified by the absence of documentation by the nurses in these charts other than to note stool type and continence status. For example, of the many headings with a pull-down menu from which one would select the desired response (see Figure 5.1), "aperients" had only two options – 'enema' or 'suppository' - and these were rarely selected. No heading for oral laxatives was provided. The only place possible to record such data was under the comments section, but historically this was mostly left blank. The purpose of an electronic bowel chart is to have accessible, standardised, accurate data to inform the clinician on bowel activity in order to make an informed decision on management. It was impossible to do this based on current documentation and the enquirer needed to be physically present in the ward with access to current drug charts and nursing notes. Perhaps the minimal documentation in the electronic chart has thus contributed to a culture of regular laxative use rather than PRN. The results from the focus group highlighted the fact that the electronic bowel chart was not a critical tool in their documentation processes and, in fact, the nurses had little time in which to complete it.(Table 5.2) Nursing in rehabilitation units is demanding and time-consuming, and has its own creative challenges with complex interactions with patients as they work towards recovery as is achievable with each patient[233].

There was no change in perception of the impact of constipation on either the nurses' work load or on the patients themselves. This is probably due in part to insufficient time to allow the bowel care plan to settle and become routine care. For change to occur, it has been recommended interdisciplinary staff have regular discussions on bowel management and institute "bowel rounds" impacting on ward culture[229]. It is also possible that in a very busy ward nurses do not generally have time to stop and think about the impact of constipation on either themselves or their patients, particularly when they had not perceived it to be a big problem in the first place. Their post implementation response may be the more accurate.

It is not always possible to have all medical staff on board with a new intervention[229], but it appears that the bowel care plan was adopted by both medical and nursing staff. It has the advantage that bowels were managed by stool type (see bowel care plan Chapter 3.4.1.1), as well as avoiding regular use of stimulant laxatives, which, when used long term, are thought to lose their efficacy, though this has not been proven[121]. This has implications for discharge planning where success of continence rehabilitation impacts on place of habitation. The use of PRN laxatives in lieu of regular laxatives provides the bowel a chance to re-develop gastro-colic reflexes as well as more opportunity for a firmer stool[231]. Overflow incontinence is associated with constipation[234], hence appropriate management contributes to continence. It has been shown that use of regular laxatives in long-term care is unnecessary and can be associated with faecal incontinence[225, 231]. In one study, withdrawal of regular laxatives saw a significant increase in frequency of bowel motions as well as a highly significant reduction in episodes of faecal incontinence[231]. Those participants were, however, part of a trial using exercise and abdominal massage to stimulate the bowel.

The advantage with using Movicol on a PRN basis is that it can be titrated up if stool type too hard, or down if stools become loose[190]. Some patients dislike the taste. Effective coercion and clever management by nurses is sometimes needed, particularly given the behavioural problems encountered in the brain injury unit. Even though it has not been built in to the care plan, the use of Osmolax, the flavourless, although not iso-osmotic, alternative to Movicol, could be explored as an option in the future. It is titrated accordingly as well, where a scoop of Osmolax is approximately equal to a Movicol sachet. The use of Dulcolax drops has the same benefit where they can be titrated as needed[192].

To date, Movicol has been contraindicated for patients with impaired swallowing. The Movicol and thickened fluid protocol is available and with the thickened fluids. (Figure 5.2) There is a paucity of

literature on the use of Movicol with thickened fluids. Starch-based thickeners lose their effect with a precipitous loss of viscosity observed when mixed with macrogol, becoming dangerously thin again[193]. Our successful use of a xanthan gum-based thickener with Movicol was consistent with the only mention of how to thicken macrogol on a Google search (Anonymous, 2017; https://precisethickn.com.au/thickening-supplements/movicol-liquid-orange-flavoured/ accessed 14/11/2017)

5.6 Limitations

The current study has limitations. First, it was not possible to show if the bowel care plan was used accurately and consistently for every patient for whom it was prescribed; the ability to assess use of the care plan remotely was not possible and required physically trolling through nursing notes and drug charts. Secondly, assessment of key patient outcomes was limited to laxative use. It will be important for future studies to examine the impact of the care plan on individual patients, such as the effect on the incidence of faecal incontinence. Being a long term, intense rehabilitation unit, 3 months is not enough time to see a change in continence status, but it would see a change in stool type had the study been so designed. Thirdly, the bowel care plan used has not been validated, it being designed by the author based on evidence for the use of the chosen laxatives. However, it was tested with different nursing staff on different wards for ease of use validating its applicability for nursing staff. Earlier studies have created their own bowel management plan according to the patient population[189, 226, 229]. A major factor in creating sustainability for a plan such as this to work really does need the creator of a new initiative or care plan to be working alongside nurses, where the ward culture needs to take ownership of the project.

5.7 Conclusions

This investigation of the implementation of an evidence-based bowel care plan was associated with improvement in management of the bowel function in an ABIU as evidenced by fewer patients on regular laxatives, documentation of laxative use in electronic bowel charts, and a change in nurse confidence in managing patients' bowels independently. It has reinforced the notion that nurses have the ability to competently manage patients with early development of constipation and prevent it from developing completely via the use of an evidence-based care plan. This study has highlighted the challenges that face nursing staff in the ability to transition to electronic documentation from hand-written data. Despite the original intention of electronic documentation to facilitate better bowel management by improved documentation, it had clearly failed in the view of the nursing staff and in the data as assessed. Using the care plan did give nurses the confidence to identify when there was potential to develop constipation and implement strategies as prescribed without having to consult a doctor every step of the way. Whether such a strategy prevents more serious problems such as impaction or faecal incontinence needs to be further addressed. Validation of the bowel care plan is needed where it has the potential for application in other hospitals and wards.

CHAPTER 6: TRANSABDOMINAL INTERFERENTIAL ELECTRICAL STIMULATION FOR REFRACTORY GASTROINTESTINAL DYSMOTILITY DISORDERS: GASTROPARESIS AND CHRONIC CONSTIPATION

6.1 Background and aims

Symptomatic functional gastrointestinal dysfunction affects about 30% of the population in the Western world[235]. A proportion of sufferers appear to have symptoms secondary to altered gastrointestinal motility. While the underlying pathophysiology of motility disorders is generally divided into neuropathic and myopathic causes, the underlying pathoaetiological mechanisms are often not ultimately determined in clinical practice as the required invasive investigations have limited clinical utility. As a result, such conditions are diagnosed by specific symptom criteria in combination with functional testing. Altered gastrointestinal motility may be regional or result in diffuse delays throughout the intestinal tract[58].

Two such conditions are gastroparesis and chronic idiopathic constipation. Gastroparesis is an upper gastrointestinal dysmotility disorder defined by delayed gastric emptying without mechanical obstruction as a cause[145]. Chronic idiopathic constipation is defined by complaints of two or more symptoms of hard, lumpy stools, infrequent stools, less than 3 times a week, straining at stool, manual or digital assistance to defaecate or a constant sense of incomplete evacuation[52]. Symptoms can

overlap with those of IBS[50, 53] and may be caused by slow-transit constipation, defaecation disorder or both.

Existing management strategies for gastroparesis and idiopathic constipation are mainly pharmacological and tended to be empirical in nature. Current therapies for gastroparesis include diet, lifestyle changes and prokinetics such as dopamine-2 antagonists, 5HT agonists, and macrolide antibiotics[91]. Therapies for constipation include diet, lifestyle changes, bulking agents, osmotic and stimulant laxatives, prokinetics and the secretagogues such as lubiprostone or linaclotide[236]. Unfortunately, all too frequently patients are either refractory to, or intolerant of pharmacological management strategies. Consequently, novel alternative therapies are sought.

Neuromodulation of the gastrointestinal tract via both the Enterra gastric pacemaker and sacral nerve stimulation are thought to have a neuroplastic effect, as discussed in Chapter 1, Section 1.3.6.2. It is postulated that transabdominal interferential electrical stimulation may be a novel, non-invasive and cost-effective means of stimulating the same neural pathways. Interferential therapy (IFT) involves the placement of two electrodes over the back lateral to the spine, and two over the abdomen at the level of the umbilicus as described in Chapters 1 and 3. These electrodes are connected to a hand-held device with which the user initiates and controls the level of stimulation. Two currents pass diagonally through the abdomen. At the point of bisection, a deeper, slow wave, therapeutic current is produced from the crossing of two slightly out of phase frequency currents with minimal activation of superficial sensory nerve fibres (see Chapter 1 Section 1.4.1)[157]. This treatment is non-invasive, painless and economical, and has been used successfully in the management of chronic pain, bladder instability and faecal incontinence with few side effects. Preliminary studies have shown the efficacy of IFT in children with refractory constipation (Chapter 1 Section 1.4.5)[152], but there is limited evidence in adults. There is also some early evidence of benefit in upper gastrointestinal conditions with one study

showing efficacy in a randomised controlled trial in functional dyspepsia[185] and case reports of benefit in refractory patients with gastroparesis.

6.2 Study aims

The aim of the study was to explore the efficacy of IFT on symptoms in a consecutive case series of adult patients with gastrointestinal dysmotility disorders (gastroparesis and chronic idiopathic constipation) refractory to conventional management strategies.

6.3 Methods

6.3.1 Participants and setting

The clinical outcomes of consecutive patients presenting to a tertiary referral centre with presumed gastrointestinal dysmotility refractory to conventional therapeutic strategies who underwent open-label IFT between October 2015 and July 2017 were studied. Patients had been diagnosed with gastroparesis and/or constipation, and were refractory to standard laxatives and prokinetic agents. They were offered the use of IFT as a novel therapeutic agent, and were taught how to use it by the author. Electrodes were placed as described in Chapter 3, based upon previous descriptions[139]. In patients with constipation, electrodes were placed bilaterally on the abdominal wall approximately halfway between the umbilicus and the lateral edge of the body and similarly on the back paraspinally between L9 and S2 on either side. In patients with gastroparesis, the electrodes were placed higher on the anterior abdominal wall just below the costal margin and mirrored thus on the back. In each situation, this resulted in 2 currents that passes diagonally anteriorly to posteriorly. As there is no evidence as to where to place electrodes, the position for gastroparesis was selected for those with both gastroparesis and constipation. Patients were advised to use the stimulation for an hour a day at around the same time. Each patient used it for a minimum of three months.

Symptoms and quality of life of patients with gastroparesis were assessed using the validated GCSI and SF-12 questionnaire at baseline and at least 3 months later. Constipation symptoms were assessed by the PAC-QOL, PAC-SYM and an overall symptom severity score by VAS at baseline and following 3 months of stimulation. These tools are described in Chapter 3.

6.3.2 Statistics

A descriptive analysis was conducted. Normality of data distribution was carried out via the Shapiro-Wilk test and parametric data were analysed via a paired t-test.

6.4 Results

6.4.1 Patients with gastroparesis

Nine patients, 7 female and median age 48 (range 23-73) years, underwent IFT as per protocol. Their individual data are shown in Table 6.1. All had significantly delayed gastric emptying on scintigraphic studies and 4 required enteral feeding. Two also had chronic constipation. Questionnaire data were available for five, 2 of whom also completed constipation questionnaires. Five patients had neuropathic gastroparesis due to either diabetes or vagal nerve injury and four idiopathic gastroparesis.

Following 3 months' abdominal stimulation, 5 patients (56%) reported clinical improvement, 2 remained unchanged and 2 had deterioration in symptoms. There was modest improvement in weight (median 3 kg) in 5 patients and a decline in 2. Weight measures were not recorded for two patients. Of the 5 patients who completed questionnaires, The GCSI and SF-12 QOL tended to improve as shown in Table 6.2. Four of the 5 patients improved in the GCSI score, but Improvement in quality of life was

seen in only three. Minor adverse events included diarrhoea in 1 patient necessitating a temporary break from use. Another increased the level of stimulation to its maximum believing more would be better, which led to muscle spasm. Following a break from using the device for a week, re-education on use given.

Table 6.1 Demographics, diagnosis and clinical outcomes of patients with gastroparesis treated with interferential therapy

Age	Sex	Diagnosis	Cause and contributing factors	Failed therapies	Weight		Outcome	Comment
					Pre-IFT	Post-IFT		
27	M	Gastroparesis	Idiopathic Bardet-Biedl syndrome	Prokinetics Dietary supplements. PEG[A] feeds	57 kg (50 kg weight loss)	71 kg	0 home TPN[B]	No response to IFT weight gain from home TPN
23	F	Gastroparesis	Idiopathic. Potential confounding factors: possible eating disorder/psychological disorder	All possible medications, NGT[C]	Varies between 34 and 62 kg. last weight 43kg	43 kg	0	Poorly tolerated. Ongoing problems.
48	F	Gastroparesis	Vagal injury post fundoplication; Pain syndrome Initial success, but developed gastroenteritis	Prokinetics, Botox injections to pylorus. All possible medications.	46 kg (26 kg weight loss)	52 kg initially. Post gastroenteritis 48kg	+	Reduced fullness on waking Slight weight gain Contracted gastroenteritis and efficacy ceased. Needed insertion of venting PEG to reduce pressure in stomach
48	F	Gastroparesis	Idiopathic: Possible multisystem atrophy	Prokinetics. Intolerant to Cisapride. Dietary supplements	67 kg (35kg weight loss).	71 kg	+++	Resolution of abdominal pain Resolution of nausea & vomiting Improved oral intake Purchased own device

52	F	Gastroparesis	Autonomic neuropathy secondary to brittle type II DM[D] On wait list for Islet cell transplant for type II DM	Prokinetics, Dietary manipulation	55 kg (15 kg weight loss)	60 kg	+++	Resolution of abdominal pain Resolution of nausea & vomiting. Improvement in oral intake Stabilisation of BSLs[E] Purchased own device
65	F	Gastroparesis Oesophageal hypomotility	Multifactorial, multiple surgery and dumping syndrome Pancreatic exocrine insufficiency	Multiple medications	Not a concern		0	No response to IFT, responded to Creon
43	M	Gastroparesis	Idiopathic	Prokinetics	Not a concern		+++	Ceased vomiting, tolerating small frequent meals; maintaining weight Ongoing benefit after ceasing therapy
26	F	Gastroparesis and slow transit constipation	Post Roux-en-Y gastric bypass	Intolerance/allergy to prokinetics. Prucalopride caused facial numbness	57 kg	60 kg after 3 weeks of IFT	+++	Increased dietary intake, reduction in symptoms, weight gain; reduction in constipation symptoms Purchased own device
73	F	Gastroparesis and constipation	Dysautonomia. Significant psychological overlay.	Multiple medications. JEJ[F] feeding tube requiring frequent replacements.	63 kg (9 kg weight loss)	65kg after 1 month of IFT	+++	Increased dietary intake, weight gain, ceased laxatives, normal stools Results did not last however. Feeding tube replaced.

0 = no response + = small response ++ = moderate response +++ = good response

[A] = Percutaneous Endoscopic Gastrostomy; [B] = Total Parenteral Nutrition; [C] = Naso Gastric Tube; [D] = Diabetes Mellitus; [E] = Blood Sugar Levels; [F] = Jejunostomy feeding tube

Table 6.2 Results of GCSI and SF-12 questionnaires in 5 patients with gastroparesis

	Pre-stimulation	Post-stimulation	P-value Paired t test
GCSI mean (SD)	30.6 (5.89)	20.2 (9.85)	0.06
SF-12 QOL mean (SD)	32.8 (8.01)	21.8 (7.91)	0.08

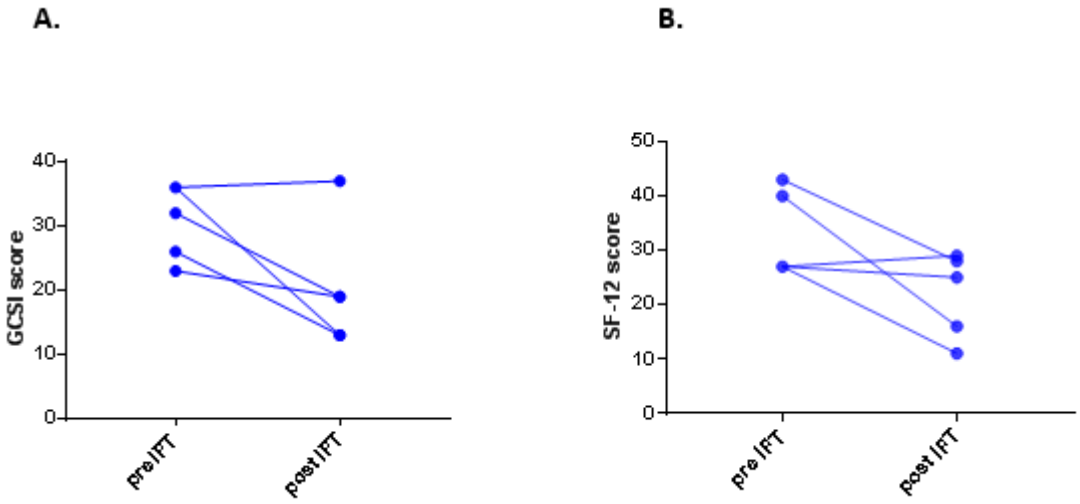

Figure 6.1 A. GCSI symptom score before and after interferentional therapy (IFT).B SF-12 quality of life scores before and after interferential therapy

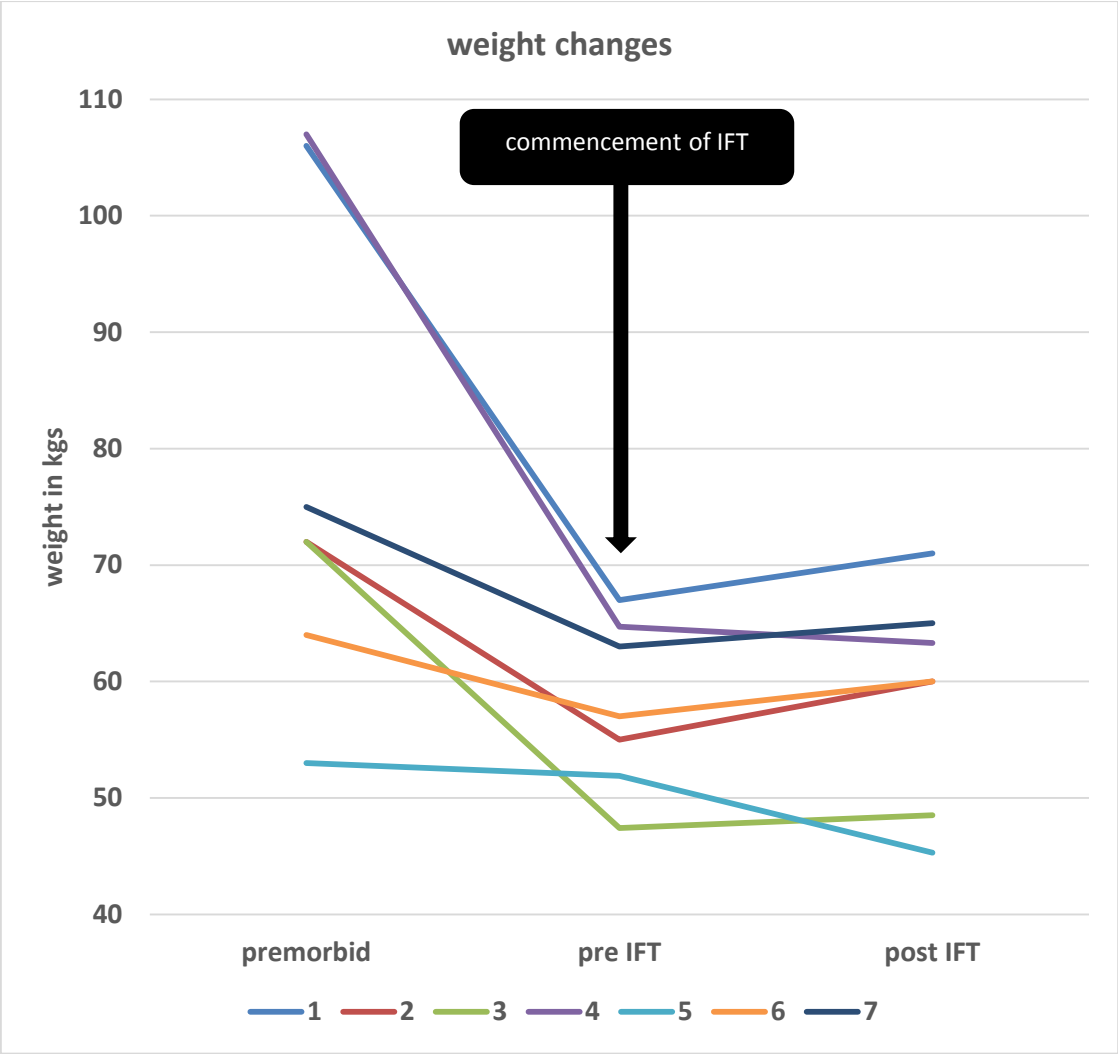

Figure 6.2 Weights prior to and at commencement of interferential therapy (IFT), and 3 months later

6.4.2 Patients with constipation

After 3 months of interferential stimulation 8 patients reported clinical improvement and 1 failed to improve. Seven reported satisfaction with stool type. Four individuals were able to cease laxative use and 3 were able to halve their use, one is currently weaning off prucalopride. One patient remained on daily laxative use despite a soft, formed stool. One patient reported no clinical benefit. Clinical benefit persisted in 2 patients post cessation of stimulation, the rest use the stimulator intermittently. There was an improvement in PAC-SYM, VAS and PAC-QOL scores as shown in Table 6.4. Eight of 9 patients improved in PAC-SYM and VAS scores, and of 6 who completed the PAC-QOL, 5 improved.

Adverse events reported were minor abdominal discomfort and diarrhoea, the latter reported in 2 patients.

Table 6.3 Demographics, diagnosis and clinical outcomes in constipation patients treated with interferential therapy

age	sex	diagnosis	cause	Contributing factors	Failed therapies	outcome	comment
26*	F	Gastroparesis and constipation – slow transit	Post Roux-en-Y gastric bypass Longstanding constipation	Constipated since infancy	Prucalopride caused facial numbness Poor response to laxatives	+++	Increased dietary intake, reduction in symptoms, weight gain; reduction in constipation symptoms. Purchased own device
73*	F	Gastroparesis and constipation	Dysautonomia	Constipating medications including opiates	Unable to swallow osmotics laxatives due to volume load and concurrent gastroparesis	+++	Increased dietary intake, weight gain, ceased laxatives, normal stools
59	M	Slow transit Constipation	McArdles syndrome Chronic LIF[A] pain	Risk of rhabdomyolosis with exercise hypertension	Intolerant to multiple medications, risk of rhabdomyolosis	+++	Ceased laxatives Resolution of abdominal pain and bloating Ongoing benefit after stopping IFT. Purchased own device
64	F	Constipation	Evacuatory dysfunction	Excessive straining weak pelvic floor Dependent on 2 sachets Movicol daily	Partial colectomy, Starr procedure	++	Halved laxative use Reduced time on toilet from 4 hours to ½ to 1 hour Awareness of gut activity
55	F	Slow transit constipation	Primary Slow transit; diabetic autonomic neuropathy Loss of urge to defaecate	Bipolar disorder, associated medications Laparoscopic gastric band surgery	Required large doses of most laxatives including Picoprep	+++	Ceased laxatives Resolution of abdominal pain and bloating Developed diarrhoea, reduced use of IFT. Purchased own device

65	F	Constipation	Primary	GORD[B], past lymphoma, left loin pain, anxiety, urinary frequency	Most laxatives. Dependant on prucalopride	+++	Ceased laxatives. Pain much reduced. Bladder symptoms relieved. Purchased own device.
58	F	Slow transit constipation	Wheelchair bound, multiple medications Fibromyalgia	Breast cancer x 2, ICU[C] early this year cardiomyopathy History of abuse	Intolerant to large dose osmotics. Dependant on prucalopride	+++	Symptom reduction >50% Reduced laxatives. Aware of borborygmi
34	F	Constipation	Connective tissue disorder Pelvic floor dyssynergia	Ehlers-Danlos syndrome, Anxiety	Sacroculposuspension Ventral mesh rectopexy	+++	Reduced laxatives. Significant improvement in symptoms and QoL[D] Occasional diarrhoea
17	F	Constipation - slow transit	Major depression ? medications Anorexia nervosa	School bullying	Intolerant of osmotic laxatives. Dependant on stimulant laxatives	0	No response

0 = no response + = small response ++ = moderate response +++ = good response

*same patient in gastroparesis section.

[A] = Left Iliac Fossa [B] =Gastro Oesophageal Reflux Disease [C] = Intensive Care Unit

Table 6.4 Questionnaire results from patients before and after 3 months of interferential therapy. Results are shown as median (IQR)

	Pre stimulation	Post stimulation	P-value (paired t test)
PAC-SYM	24 (18 – 34)	14 (10-21)	**0.001**
PAC-QOL	86 (76-93)	50 (32-64)	**0.01**
Symptom VAS	85 (77-92)	50(30-62)	**<0.0001**

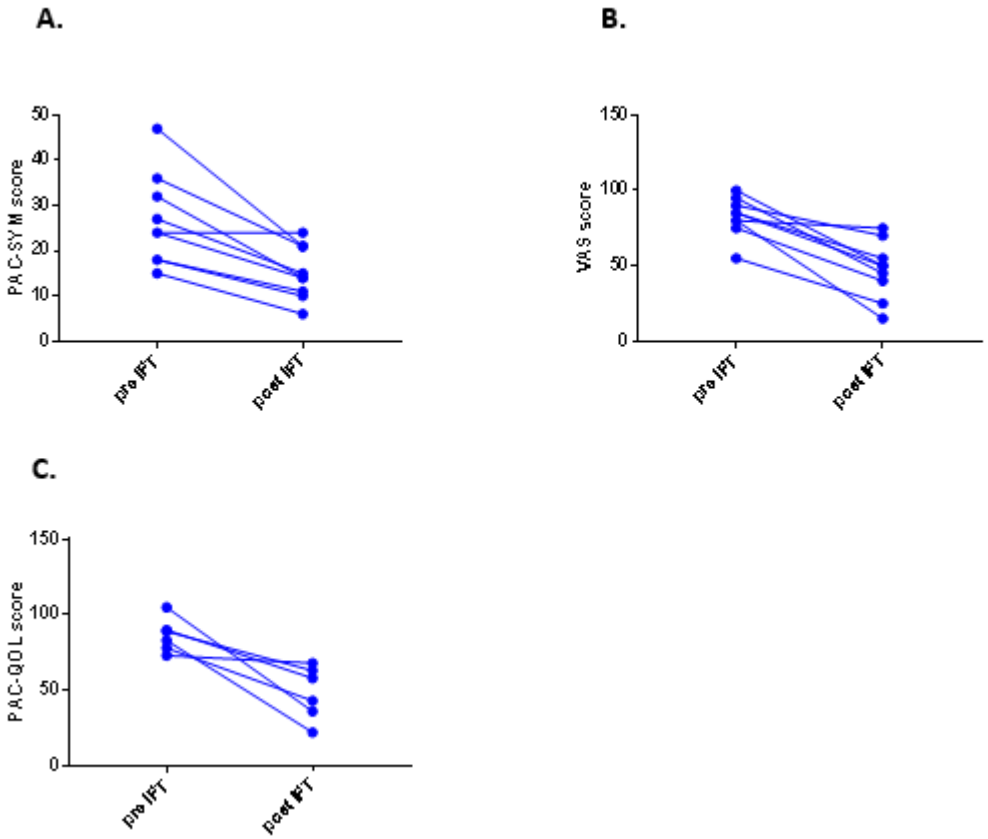

Figure 6.3A. PAC-SYM score before and after 3 months of interferential therapy (IFT) B. VAS symptom score before and after interferential therapy (IFT) C. PAC-QOL score before and after interferential therapy (IFT)

6.5 Discussion

Therapy is challenging in many patients with chronic motility issues such as gastroparesis and constipation. The notion of non-pharmacological approaches is appealing, particularly as drugs are not curative and provide symptoms relief only as long as they are taken. Non-invasive neuromodulation via IFT has apparent benefits in children with constipation, and case reports and series in adults with those conditions have suggested efficacy. The current study reports a small series of patients with both conditions who, despite being refractory to other therapies, showed a reasonable rate of response. Thus, 5 of 9 patients with gastroparesis responded well to IFT and bowel symptoms and QoL improved in 8 of 9 patients with constipation. Adverse effects were minor, diarrhoea being an expected adverse effect, and resolved on cessation.

Four of the five patients with gastroparesis who reported clinical benefit had a neurogenic cause of gastroparesis. Whether the pathogenesis of gastric dysmotility may act as a predictor for response cannot be ascertained, but deserves further evaluation. The pattern and chronology of response seemed to mimic that reported in patients who have undergone gastric electrical stimulation (GES). Thus, patients reported that a feeling of fullness on waking was the first symptom to be alleviated, followed by a marked reduction in vomiting. These observations suggest that both modalities might be working via similar patholaetiological mechanisms[237]. The therapy also appeared to be having effects on more distal motility since diarrhoea was reported in 3 patients, and two others who had concomitant constipation improved.

The response in bowel symptoms and QoL in patients with chronic constipation was excellent with 88% improving. This was very similar to the 90% who improved in a previously-reported paediatric cohort[181]. The high success rate possibly related to the ability to use the device at home and for an

extended period where earlier paediatric studies had participants attend hospital several times a week for treatment. Results were less impressive though still positive[162, 176, 181].

The fact that almost all the patients in the constipation group improved suggests a high placebo response may be occurring. In the paediatric study in which IFT was used in the child's home environment, there was concern that regular contact by telephone every 2 to 3 days for several weeks to ensure they were comfortable with the treatment might have led to a higher placebo response[181]. In the present study, patients were not contacted routinely, except for an occasional email, so regular contact was unlikely to be a driver of a placebo response. The Turkish study of patients with functional dyspepsia noted a high placebo response where there was considerable interaction with the therapist[185].

The heterogenous nature of gastrointestinal motility disorders is also confounded by the number for whom the exact aetiology of dysmotility is unknown, which makes it difficult to predict what kind of therapeutic action may have benefit[238, 239]. The autonomic neuropathies which include diabetic gastroenteropathy or surgically-induced nerve damage associated with delayed gastric emptying are particularly challenging[239]. Neuromodulation is a new therapeutic strategy and appears to have potential in some of these conditions. Our finding that those with a neuropathic cause of their delayed gastric emptying seemed to be more likely to respond to stimulation raises the possibility that the underlying pathophysiology might enable targeting of therapy, but further study is required before the notion that the phenotype of patients based on physiology can be considered helpful for targeting therapeutic interventions.

How IFT acts on the GI tract is poorly understood. Some investigators have suggested the effects might represent neuroplastic events, where there may be stimulation of the interstitial cells of Cajal and the

enteric nervous system, or of autonomic nerve fibres in the spinal cord rather than direct action on the muscle fibres[162]. A muscular response would see more of an "on-off" behaviour in contrast to the observed response whereas in paediatric studies a prolonged clinical response was observed after ceasing its use. Furthermore, transit times were significantly decreased and an increase in propagating sequences, have been reported[162]. In the present study, at least 2 in the constipation group had ongoing benefit long after ceasing its use. The placement of the electrodes in relatively close proximity to the spinal cord may affect both afferent and efferent pathways[165]. A hormonal response is also possible if IFT is able to stimulate production of endorphins[167], but this suggestion has yet to be supported by evidence.

Lessons regarding mechanism of action might also be gleaned from those where there was no response to IFT. The first observation was that those without clear neuropathic cause and strong psychological overlay to symptoms and/or complex comorbidities did not respond. All too frequently psychosocial concerns underlie functional GI symptoms with abnormal illness behaviour common in those with issues of constipation and/or gastroparesis[28]. For example, in the present study, the 17 year old girl with constipation had significant anxiety and depression issues to the extent she could not attend school. Likewise, the three non-responders with gastroparesis also had psychological co-morbidities that were complex and not neurogenic in origin. Secondly, a structural cause might underlie non-response, for example, one patient had severe adhesions following several catastrophic surgical events that may have hindered attempts to improve gut motility.

The current study is a case series that raises the potential for IFT to be a useful therapeutic strategy. The number of patients were small, as were those in the study by Yik et al exploring the use of home-based therapy[181]. A couple of studies have investigated the role of IFT in upper GI dysmotility disorders with some degree of success[181, 185]. More work has been done however on constipation with significant

success, in particular with children[152, 180] though few have been randomised controlled trials. More placebo-controlled trials are needed. More work is needed on the impact of IFT on neurogenic and/or idiopathic dysmotility disorders leading to studies investigating predictors of success. Studies that measure physiological responses to IFT are needed to better understand the mechanisms of action.

6.5.1 Conclusion and future directions.

Interferential electrical stimulation results in significant symptom improvement and improved quality of life in patient with intractable chronic idiopathic constipation. There is also a signal that IFT may be helpful in patients with gastroparesis, particularly if there is an underlying neurogenic cause. While there is likely to be a significant placebo effect, IFT appears safe and well tolerated, and is likely to be more cost effective than existing invasive neuromodulation therapy. This case series justifies further exploration in a blinded placebo controlled trial to more formally assess efficacy.

CHAPTER 7: DETERMINING THE EFFECTIVENESS OF TRANSABDOMINAL ELECTRICAL STIMULATION IN THE TREATMENT OF FEMALE ADULT PATIENTS WITH CONSTIPATION – A RANDOMISED CONTROLLED TRIAL.

7.1 Background and aims

Constipation remains a difficult problem to treat, affecting about 15% of the population with significant morbidity and reduced quality of life in addition to direct and indirect economic impact[49]. Management of constipation has historically depended on a variety of strategies beginning with lifestyle advice addressing dietary fibre and fluid intake, followed by the use of laxatives, both osmotic and stimulant. However, there are patients with chronic constipation who experience difficulty in managing symptoms despite appropriate interventional strategies[50]. Neuromodulation is a relatively recent novel means of treating constipation and is thought to modify organ function via electrical stimulation of neural pathways[240]. Sacral nerve stimulation (SNS), the most established form of neuromodulation, involves low-dose neural stimulation of the sacral nerve roots via permanently implanted electrodes placed through the sacral foramen at the level of S2 to S4[135]. SNS is invasive and expensive, requiring two general anaesthetics and surgical procedures. Given these limitations, SNS is rarely used clinically.

Another form of neuromodulation, interferential current therapy, has recently evolved to treat symptoms of constipation and faecal incontinence[188]. It is administered transcutaneously via transabdominal electrical stimulation, also known as interferential therapy (IFT) as described in Chapters 1 and 6. While an exciting prospect, the evidence-base for efficacy of IFT in chronic constipation is limited. Observational studies, like that by Queralto et al[98] or our own experience described in Chapter 6, show promising efficacy. Randomised controlled trials have suggested efficacy in children[152, 162, 180] and, more recently, in an adult population with slow-transit constipation[184]. However, the limitations of these studies are considerable. They include lack of an adequate placebo, small sample size and a lack of objective measures, participants also required to attend the hospital for treatment sessions[184, 186]. Participants were also banned from rescue laxatives.

Hence, the aims of this pilot study were to determine the short and long-term efficacy of home used IFT by performing a single-blind, placebo-controlled in adult women with constipation and in doing so determine whether a unique, novel placebo that does not affect blinding is successful.

7.2 Materials and methods

7.2.1 Participants

Female participants were recruited through the Monash University clinical trials website, via gastroenterology outpatient clinics and via social media from January 2015 to July 2017. Subjects must have experienced less than or equal to 2 spontaneous complete bowel actions a week for at least 6 months, and, at least 25% of the time one of hard lumpy stools, a sense of incomplete evacuation or a need to strain during defaecation. Participants who met inclusion/exclusion criteria were included as described in chapter 3.1. The study was conducted pragmatically and thus patients could continue laxatives although daily intake was monitored via means of a bowel diary.

The study was conducted at The Alfred Hospital in Melbourne, Australia.

7.2.2 Protocol

The study was a single-blind, placebo-controlled pilot study. Participants meeting inclusion criteria were interviewed by the study doctor where consent was obtained. A two-week bowel diary and a questionnaire comprising the PAC-SYM, PAC-QOL plus a visual analogue scale (VAS) of the severity of constipation from 0 to 10, was given, as outlined in Chapter 3.5. Randomisation was performed using a computer-generated random list creating sealed envelopes that, on opening, indicated one of two arms. The participant and all but the co-ordinating investigator were blinded to the arm. The two arms were:

- Interferential therapy: Electrodes were placed anteriorly on the abdomen and posteriorly on the back just above the level of umbilicus anteriorly and between T9 and L2 posteriorly on the mid-clavicular line where the 2 currents ran diagonally through the abdomen to the back, right front to left back and vice versa (Figure 7.2).
- Sham therapy: The electrodes were placed anteriorly and posteriorly as for the interferential current, but the currents did not cross, and thus ran laterally, right front to right back and left front to left back (Figure 7.2).

Therapy continued as taught for one hour per day at the same time of day for 6 weeks. At the conclusion of the 6-week period, the IFT device was returned. Two weeks prior to commencing the study participants completed a 2-week bowel diary and questionnaire. This was repeated 3 weeks into the study, at the end of the 6 weeks, 3 months after conclusion of the study and at 1 year.

The protocol was approved by Alfred Health, Ethics and Research Governance; project no: 282/14

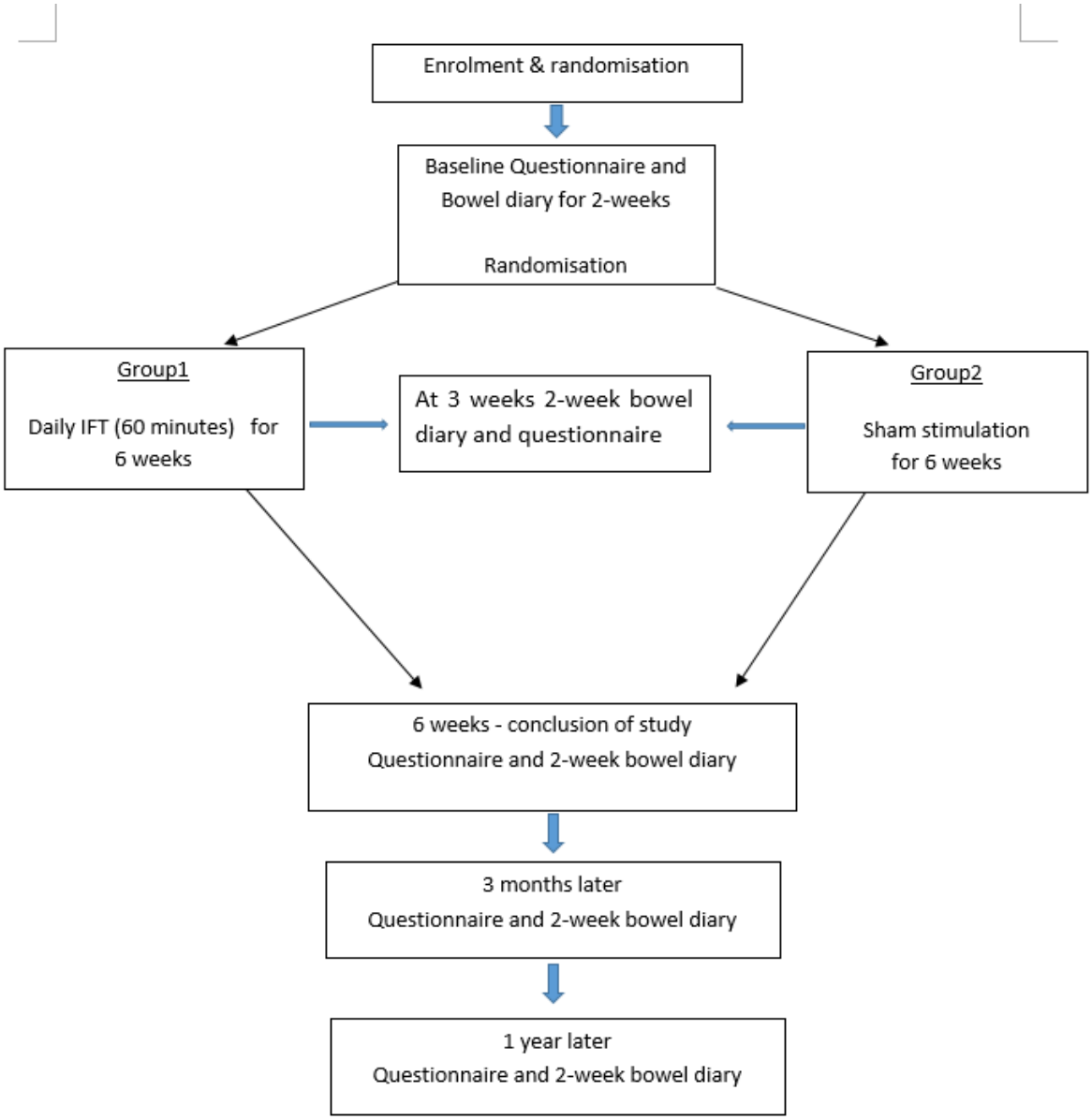

Figure 7.1 Study Protocol: Determining the effectiveness of transabdominal electrical interferential stimulation in women with constipation

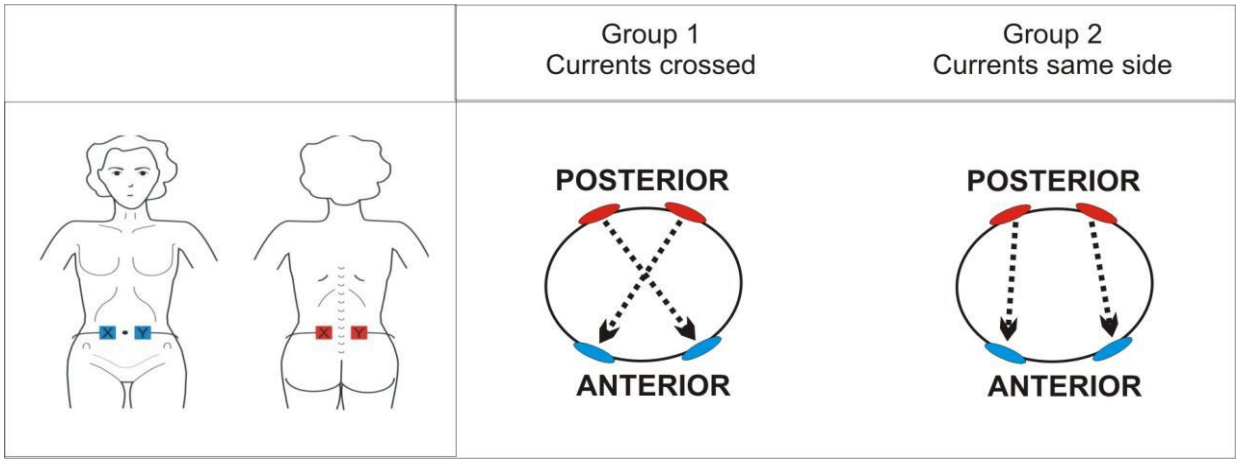

Figure 7.2 Connection of electrodes for group 1, interferential stimulation, and group 2, sham stimulation

7.2.3 Measurements

7.2.3.1 Constipation symptoms

Patient symptoms were assessed via the use of the PAC-SYM questionnaire as described in Chapter 3, section 3.5.3. This was completed before randomization into the study, at 3 weeks into the study, at the end of use of the stimulation at 6 weeks, 3 months after completing the study and at 1 year after completing the study. Overall severity of constipation was measured via a 100 mm (VAS) at the same time points.

7.2.3.2 Quality of life

Quality of life was assessed via the PAC-QOL as described in chapter 3. It was completed at baseline, after 3 weeks of stimulation, and at the conclusion of the 6 weeks of stimulation, at 3 months' post completion of stimulation and at one year.

7.2.3.3 Bowel diary

Participants kept a bowel and laxative diary for 2 weeks prior to the therapy. They were asked to continue the diaries for another 2 weeks half way through the therapy and for a further 2 weeks post

completion. Follow up two week diaries were sent to participants to complete at 3 months and 1 year post-treatment.

7.2.4 Endpoints

The primary end-point was the number of participants with more than 2 spontaneous bowel movements per week by the end of the 6-week study period. "Spontaneous" means without the use of laxatives to achieve this.

Multiple secondary end-points were examined. These included:

- The proportion of participants with >2 spontaneous complete bowel movements per week;
- change in severity of the constipation symptom score, the PAC-SYM, as described in Chapter 3.5.5;
- the proportion of participants that had a clinical improvement ≥1 point in the PAC-SYM[197];
- change in severity of constipation symptoms as rated by the VAS scores, as described in Chapter 3.5.7;
- the proportion of participants who had a reduction in the severity of constipation symptoms as rated by the VAS score by 20 mm or more;
- change in the PAC-QOL score, as described in Chapter 3.5.6;
- the proportion of participants who had an improvement ≥1 point in the PAC-QOL[197];
- the proportion of participants who had a reduction in laxative use by more than 50%;
- the proportion of participants who had a reduction of the incidence of straining by more than 50%;
- change in individual symptom scores in the PAC-SYM.

7.2.5 Compliance

Compliance with the therapies as instructed were not directly assessable and relied upon direct questioning of the participants via email or phone calls. An email was sent to participants 3 weeks into use of treatment to remind them to complete the questionnaire and 2 week bowel diary as well as enquiring about their use of the machine. The aim was to ensure a maximal completion rate as well as checking there were no concerns or problems with the machine and to remind them to stick to the same time of day. Further contact was minimal to avoid a placebo response. Compliance was assessed indirectly via by completion of the 2-week bowel diary and a questionnaire commencing at the 3rd week of treatment.

7.2.6 Adverse events

Participants had access to the study coordinator's mobile phone and email and were instructed to alert her if there were any concerns. Adverse events were documented by direct questioning of the participants at study visits and telephone calls. Those reported were assessed by the study doctor, and classified with regards to severity, the participant examined by the study doctor if necessary and likely relationship to the treatment deemed as probable, possible or unrelated. They were reported to the Ethics Committee as per the Alfred Health Ethics protocol.

7.2.7 Statistical Analyses

As this was a pilot study, power calculations were not performed, but it was planned for to recruit 50 participants, becoming 44 after allowing for a 20% drop out in both groups. An intention-to-treat (ITT) analysis was performed on randomised subjects who had baseline data, had at least 1 week of treatment and had any evaluable data after treatment started. A per-protocol (PP) analyses was also conducted. As nearly all continuous indices measured were not normally distributed, results were

expressed descriptively as median and Interquartile range (IQR). Analyses were performed using Graph Pad Prism (version 6.0 for Windows, Graph Pad Software, La Jolla California USA). Response rates were compared using Fisher's exact test. Differences between the two groups were analysed using a Mann-Whitney U-test and measured variables in the same group analysed via Wilcoxon signed rank test. P-value was set at ≤0.05 except where a Bonferroni correction for multiple comparisons was applied.

7.3 Results

7.3.1 Participants

Participant recruitment is shown in Figure 7.2. Of 82 participants screened, 19 were not interested after receiving a formal copy of the participant information and consent form for their perusal and 18 did not meet the entry criteria on initial screening. Of the 10 who withdrew before commencement of the study, 3 withdrew for health reasons and 7 were no longer interested. No pre-study data were provided by 1 subject and all data from 1 who completed treatment did not arrive after being posted. Thus, 33 participants were included in the ITT analysis and 31 the PP analysis.

The first 9 participants did not receive a complete PAC-QOL questionnaire. At the time of analysis for the thesis, data at the 3-month time point post-intervention was available for 12 participants in the IFT group and 10 in the sham. These data were presented only as PP analysis. There is yet insufficient data to examine the 1-year time point.

7.3.1.1 Baseline data

Women in both groups were compared for age and pre-study spontaneous bowel movements per week, spontaneous complete bowel movements per week, PAC-SYM, VAS and PAC-QOL scores where there was no difference between the two groups.

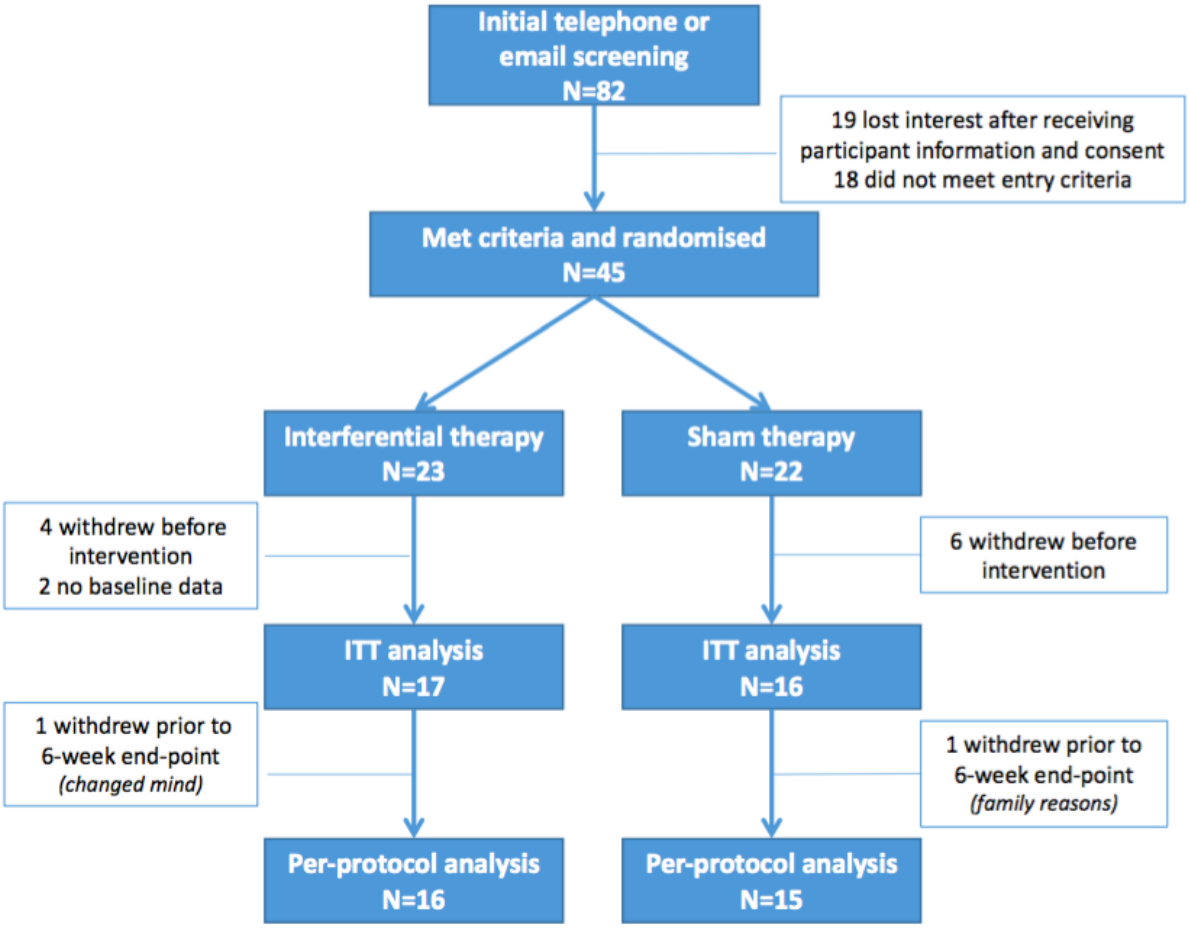

Figure 7.3 Flow diagram of participants involved in the study

Table 7.1 Comparison of the 2 groups for age and primary and secondary outcome scores pre-study using the intention to treat (ITT) analysis. All data are expressed as median (IQR) except where indicated.

	Interferential therapy N=17	**Sham therapy N=16**	**P-value** Mann-Whitney U
Mean age (range) years	45 (19-67)	44 (23-66)	0.7*
Number of spontaneous bowel movements per week	0 (0-2)	0 (0-3)	0.6
Number of spontaneous complete bowel movements per week	0 (0)	0 (0)	>0.9
PAC-SYM score	26 (19-31)	24 (20-29)	0.7
Constipation symptom severity (100 mm visual analogue scale)	80 (65-85)	75 (61-85)	0.6
PAC-QOL score	64 (58-76)	67 (55-83)	0.9

* Wilcoxon signed rank test

7.3.2 Effect on primary and secondary outcomes.

Nine of 17 (53%) in the IFT group met the primary outcome of achieving more than 2 spontaneous bowel movements per week compared with 2 of 16 (12%) in the sham group (ITT analysis; P=0.02; Fisher's exact test). For the PP analysis, 9 of 16 (60%) receiving IFT therapy compared with 2 of 15 (13%) with sham therapy met the primary end-point (p=0.02). (Table 7.2)

The effects of therapy for the secondary endpoints in both ITT and PP cohorts are shown in Table 7.2. The change in PAC-SYM scores, the proportion of participants with a reduction in constipation severity as judged by the VAS score ≥20 mm were greater in the IFT group than the sham group. Also the

proportion of participants with a reduction in laxative use ≥50% a week were significantly greater in the IFT group than the sham group in both the ITT and PP analysis. (Table 7.2) There was no significant change in outcomes of a reduction in PAC-QOL score, a reduction in straining by ≥50% over a week, or the number of spontaneous complete bowel motions a week between the IFT group and the sham group.

To date, twelve in the IFT group and 10 in the sham group have completed questionnaire and diary data at the 3-month time point. At the 3-month time point, 7 (58%) in the IFT group continued to achieve more than 2 spontaneous bowel movements a week vs 1 (10%) in the sham group. (P=0.03) (Figure 7.4 B) Three in the IFT group (25%) maintained an increase in the number of spontaneous "complete" bowel movements vs 1 (10%). (P=0.5) (Figure 7.5 D) There was still a significant reduction in the PAC-SYM score with the median change (IQR) in the IFT group of 8 (5-19) vs 0 (-2-8) in the sham group. (P=0.02). (Figure 7.6) A change in constipation severity VAS score at 3 months was also significant at P=0.03. Median change (IQR) 20 (2.5-36) vs 5(-2.5-11) sham group. (Figure 7.7) Three months after completing use of the stimulator there was a significant change in PAC-QOL scores from pre-stimulation, median change (IQR) 27 (12-33) in the interferential group vs 4 (-2-7) in the sham group (P=0.001).

The proportion of participants who were deemed responders for the PAC-SYM at 3 months were 50% in the IFT group vs 10% (P = 0.07ns). The proportion of those who maintained a response in the constipation VAS 3 months after stimulation was 58% in the IFT group vs 10% in the sham group (P = 0.03). At 3 months, the number of responders to the PAC-QOL was 6 (75%) vs 0%, P=0.009. There was a reduction in straining maintained in 2 (16%) in the IFT group with 1 in the sham, P=>0.9, and a reduction in laxative use was maintained in 4 (33%) in the IFT group but none in the sham group, P=0.09.

Analysis of individual symptoms within the PAC-SYM showed a significant improvement in all individual symptoms in the actual group, and in one symptom, pain on defaecation, in the sham group (Table 7.3).

7.3.2.1 Compliance to therapy

Participants responded to the reminder emails at 3 weeks where they reported no problems in using the machine. One participant had technical failure of the machine and commencement of the therapy was, therefore, delayed 1 week until the machine was replaced. The majority of participants appeared to have been compliant based on the submission of the 2-week diary and the questionnaire from the 3rd week where 1 only in both groups failed to submit a diary for that point. These particular 2 participants did, however, complete the diary and questionnaire at the end of the study. There were data at the 3 week time point from 1 participant who withdrew before completion of the study, but not for the other. Two did not return their diary at 6 weeks, but completed data at the 3 month time point. It is presumed they went missing in the post.

7.3.2.2 Adverse events

The use of stimulation, both IFT and the sham treatments, were well tolerated in general. One patient in the IFT group developed gastroenteritis. It resolved spontaneously and was not considered related to the therapy. No other participants in the treatment or sham groups developed diarrhoea. One patient died due to suicide during follow-up about a week after ceasing treatment. At her final visit she spent about an hour talking with the study doctor about her concerns that constipation had not been relieved, and while she appeared anxious there was no indication she was suicidal. She had significant psychological issues that had been undisclosed at recruitment. She was in the IFT group, but had no improvement in symptoms.

Table 7.2 The effects of interferential therapy (IFT) or sham therapy in female patients with chronic constipation on clinical measures and quality of life after 6 weeks of treatment. Results are shown as per the intention-to-treat and per-protocol cohorts

End-points	**Intention-to-treat analysis**			**Per-protocol analysis**		
	IFT N=17	**Sham** N=16	P value	**IFT** N=16	**Sham** N=15	P value
Number (proportion) of participants achieving more than 2 spontaneous bowel movement per week	9 (52%)	2 (12%)	**0.02***	9 (60%)	2 (13%)	**0.02***
Number (proportion) of participants achieving more than 2 spontaneous complete bowel movements per week	6 (35%)	1 (6%)	0.08*	6 (40%)	1 (7.1%)	0.07*
Change in PAC-SYM score from baseline Median (IQR)	8 (1.5-15)	2 (0-9.5)	0.07**	8 (4-16)	3 (0-11)	**0.03****
Change in severity of bowel symptoms (100-mm visual analogue scale) from baseline Median (IQR)	20 (0-47)	0 (-8-20)	0.05**	25 (0-50)	0 (-10-20)	**0.04****
Change in PAC-QOL score from baseline Median (IQR)	26 (4.5-49) (n=12)	0 (-10-6) (n=11)	0.1**	28 (15-52) (n=11)	6 (0-26) (n=10)	0.06**
Proportion who reduced straining events by ≥50% per week	5 (29%)	1 (6.25)	0.1*	5 (33%)	1 (7.1%)	0.16*
Proportion who had reduced laxative use ≥50% per week	10 (58%)	2 (12%)	**0.01***	10 (66%)	2 (14%)	**0.007***
Proportion with reduction in PAC-SYM score by ≥1	7 (41%)	3 (18%)	0.2*	7 (46%)	3 (20%)	0.2*
Proportion who had a reduction ≥ 20mm in symptom VAS	10 (58%)	5 (31%)	0.16*	9 (60%)	5 (33%)	0.2*
Proportion who had a mean reduction in score by ≥1 point in PAC-QOL	7 (41%)	2 (12%)	0.11*	7 (57%)	2 (20%)	0.09*

* Fishers exact test ** Mann-Whitney U test

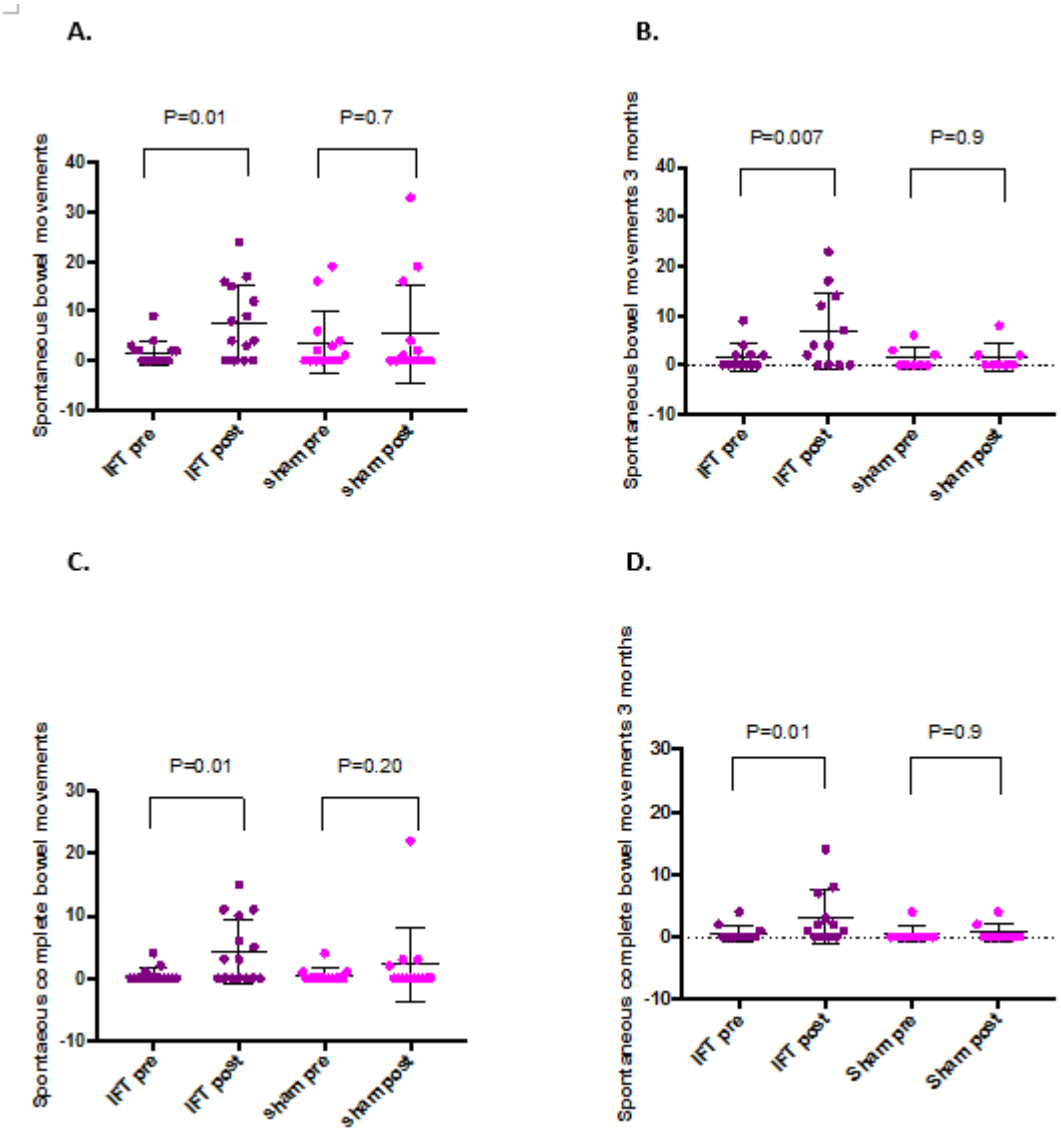

Figure 7.4 Comparison of bowel movements during the baseline and during and 3 months after interferential (IFT) or sham therapy. A. The number of spontaneous bowel movements at 6 weeks; B. The number of spontaneous bowel movements at 3 months; C. The number of spontaneous "complete" bowel movements after 6 weeks of treatment; D. The number of spontaneous "complete" bowel movements at 3 months. Statistically significant differences in paired data were observed for all indices in the IFT but not the sham group at both time points. All values shown are for per protocol analysis (Wilcoxon signed rank test)

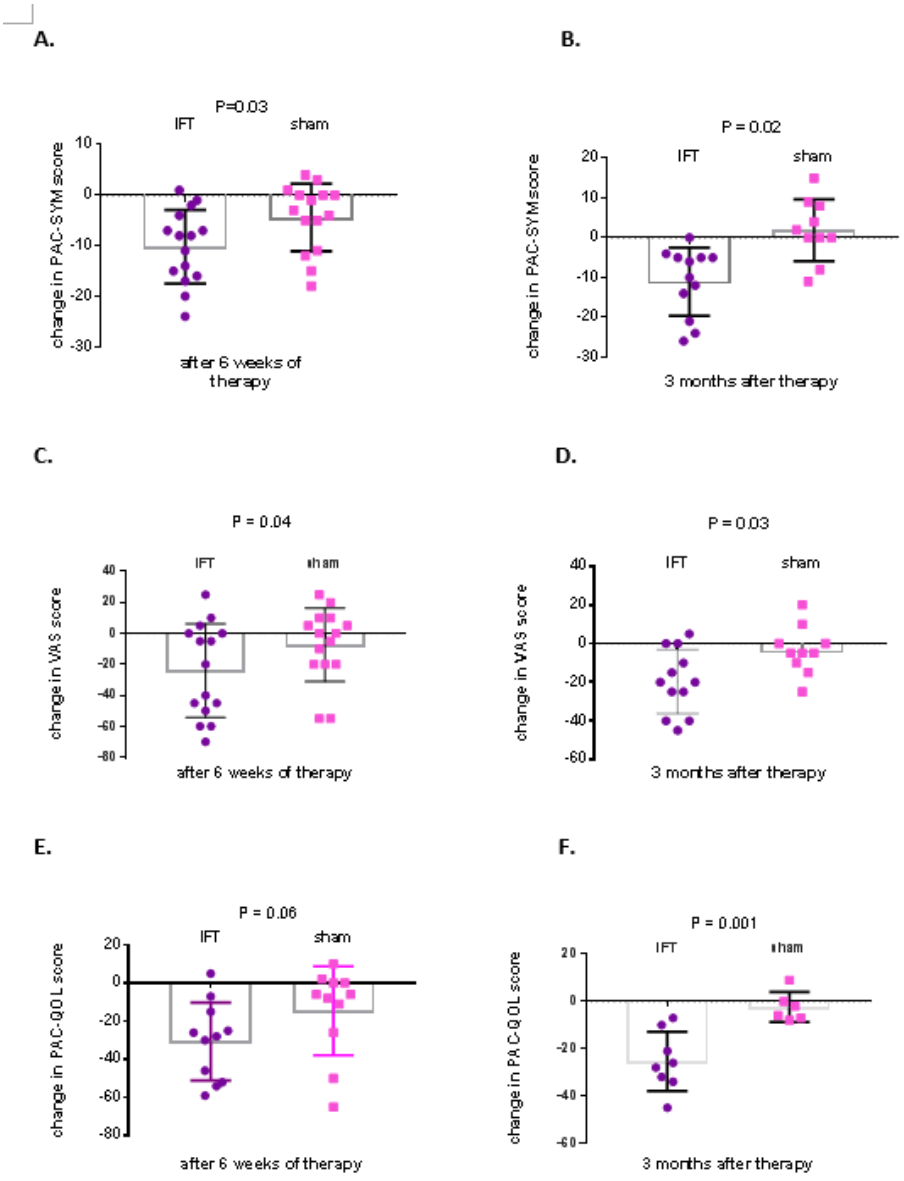

Figure 7.5 Comparison of the change from baseline in the PAC-SYM score, severity of bowel symptoms via 100-mm visual analogue scale (VAS) PAC-QOL scores in individual patients during and 3 months after interferential (IFT) or sham therapy. A. Change in PAC-SYM score after 6 weeks of treatment, B. Change in PAC-SYM score 3 months after ceasing treatment; C. Change in severity of bowel symptoms after 6 weeks of treatment; D. Change in severity of bowel symptoms 3 months after ceasing treatment; E. Change in PAC-QOL score after 6 weeks of treatment; F. Change in PAC-QOL score 3 months after treatment. Statistically significant differences were observed between the treatment groups for all indices at both time points except for PAC-QOL at 6 weeks. All values shown are as per protocol analysis (Mann Whitney U test)

Table 7.3Median (IQR) response scores of individual symptoms in PAC-SYM before and after interferential therapy. Each component was rated via a Likert scale from 0 to 4, where 0 = no symptoms and 4 = worst possible. Statistical comparison was made using a Wilcoxon signed rank test and the P value was set at 0.004 after Bonferroni correction. P values for both per protocol (PP) and intention to treat (ITT) analyses are shown

	Interferential therapy			**Sham therapy**		
	Pre	Post	P-value ITT/PP	Pre	Post	P-value ITT/PP N=16/n=15
Discomfort	3 (2-3)	2 (1-2)	0.01 / 0.01	3 (2-3)	2 (1-3)	0.07 / 0.07
Abdominal pain	2 (2-3)	1 (0-2)	0.005/0.009	2 (2-3)	2 (1-3)	0.09 / 0.09
Bloating	3 (2-3)	2 (1-3)	0.03 / 0.03	3 (2-3)	3 (2-3)	0.09 /0.09
Cramping	2 (2-2)	1 (1-2)	0.03 / 0.002	2 (1-3)	2 (1-3)	0.6 /0.6
Pain on defaecation	2 (1-3)	1 (0-1)	**0.002/0.02**	2 (0-2)	0 (0-2)	0.03 / 0.03
Burning in rectum	2 (1-3)	1 (0-1)	**0.002/0.002**	2 (1-2)	2(1-2)	0.3 / 0.3
Bleeding from rectum	1 (1-2)	1 (0-1)	0.03 / 0.03	1 (0-1)	1 (0-1)	0.18 / 0.18
Incomplete evacuation	3 (3-4)	2 (1-3)	**0.001/0.001**	4 (3-4)	2 (2-4)	0.06 / 0.06
Hard stools	2 (1-3)	1 (1-2)	0.04 / 0.1	2 (1-3)	1 (1-2)	0.19 / 0.19
Small stools	2 (2-3)	2 (1-2)	0.007/0.02	2 (2-3)	2 (1-3))	>0.9 / >0.9
Straining	3 (2-4)	2 (1-2)	**0.002**/0.01	2 (2-3)	3 (1-3)	>0.9 / >0.9
False alarm	2 (2-3)	1 (0-2)	**0.0005/0.0005**	2 (1-3)	1 (1-2)	0.5 / 0.5

7.4 Discussion

This pilot study provides strong evidence that transabdominal IFT improves bowel function in chronically constipated women. Not only was there was an improvement in the primary endpoint of more than 2 spontaneous bowel motions a week at the end of 6 weeks' therapy in more than on half of patients in the IFT group compared to one in 8 in the control group, but also the data currently available suggest this was maintained 3 months later. Other, but not all, measures associated with constipation including perceived severity of bowel symptoms as in the PAC-SYM, the constipation severity VAS score and laxative use were also significantly improved in the IFT group, suggesting that the benefits were real. Although quality of life only tended to improve more with IFT than sham therapy when measured at 6 weeks, a clear improvement was observed after a further 3 months, due to both persistence of the benefits of IFT and loss of the likely placebo benefits of the sham treatment. Moreover, the therapy was well tolerated with no adverse events judged related to the therapy itself. Thus, the findings support IFT as a safe, non-invasive means of treating symptoms of constipation in adult women.

The outcomes of this study sit well within the existing literature in this field, although there were differences in how the treatment was delivered and how the response was measured. In 2 previous RCTs in adults, participants received 20-minutes' treatment at the hospital, 3 times a week for 4 weeks only rather than daily at home stimulation[184, 186], compared with daily, 1-hour self-administration. It is tempting to attribute the various improved symptom scores and an increase in bowel motions per week better responses to these differences in exposure time and the at-home delivery of the IFT. The end-points used in the current study were more comprehensive than those used in previous studies. Most importantly, our assessments included spontaneous and complete bowel actions, not just the number of bowel actions per week. A sense of incomplete evacuation is a common complaint in constipation, one that is not often assessed. Moreover, our data are shown so that both individual

responses and percentages of participants with a positive response are clearly presented. Such information is difficult to tease from studies that only show an overall improvement in the reported outcome. It is difficult to know, therefore, whether such studies had a small group of people improve significantly, or a lot improve a little. Our other endpoints, were similar to that of other studies in assessing symptom severity and quality of life[98, 179, 184, 241], but we included not only the number of people who responded to treatment, but also a comparison in changes in scores. Finding significant improvements in the IFT group across multiple methods of assessing symptoms associated with constipation is reassuring that IFT is a successful, novel intervention in treating constipation, supporting findings from other studies[98, 139, 152].

The fact that improvements in the primary and secondary endpoints were maintained over the 3-month follow-up period, as also found a paediatric study where up to 37% still had symptom relief more than 2 years post treatment cessation[188]. This was also observed in 1 of 2 adult RCTs where symptom VAS scores continued to decrease a month after treatment had finished[186]. Obviously 3 months is still a short time frame, hence data collection for this study is ongoing and we expect to have 1 year follow up data completed at the end of 2018. It must also be noted that the number of participants providing data at the 3-month period is reduced, where nearly a quarter are still to return their questionnaires and diaries. This means that the current 3 month results are incomplete and could well change.

As seen in paediatric studies, there was a significant drop in laxative use. A number of studies ban or significantly restrict the use and type of laxatives during their study[162, 186, 241]. While this may show categorically that positive results are not at risk of being due to a therapy other than IFT, it does place the participant in a potentially uncomfortable or unpleasant study period. Our study permitted use of concurrent laxative use, but participants were asked to only take laxatives on an as needed basis. We

did see a significant drop in laxative use in both the ITT and PP analysis with 66% in the IFT group vs 14% in the sham group drop their laxative use by more than 50% at the 6-week time point. This did, however impact on the ability to collect data on stool consistency, as the use laxatives may have affected stool form. The lack of reduction in straining is not surprising. Straining is a learned, habitual behaviour and contributes to a dyssynergic pattern of defaecation that can result in constipation[22]. Home use of stimulation alone is not likely to make a difference to this outcome within the time frame it was used, where more favourable results would likely occur with concurrent biofeedback, a successful means of treating constipation caused by pelvic floor dysfunction[131].

While the effect on quality of life of IFT therapy at the end of 6 weeks was not statistically significant, there was a clear trend of an improvement in the PP cohort (Figure 7.5 F). Interestingly, the improvement in PAC-QOL score at the 3-month mark in the IFT group became statistically significant (P=0.001). This may be the result of the placebo effect where those in the sham group who had an improved quality of life at 6 weeks, deteriorated by the 3-month time point whereas those in the IFT group maintained their benefit. An explanation for this is that there was little or no contact with the study coordinator after ceasing use of the device at the end of 6 weeks. In order to minimise a placebo effect being induced by unintended therapeutic interactions by the study coordinator, there was minimal contact with study participants during the 6-week period other than to remind participants of appointments or to complete and return study questionnaires. It has been reported that clinical trials in patients with functional gastrointestinal disorders are more susceptible to a placebo response in the actual treatment group and a nocebo effect in the sham[242]. Because of this risk with the study coordinator not being blinded, every step was taken to minimise this. However, it is possible minimal contact contributed to the low placebo response, where 13% in the sham group achieved the primary outcome of more than 2 spontaneous bowel movements a week. While this response appears low in comparison to some trials[197] it has been noted in an integrated analysis of 6 randomised controlled

drug trials their placebo response was comparable at 13.2%[243] indicating that our placebo was a valid one.

A key aspect of the current study was the assessment of a novel placebo, where the sensation of stimulation was similar to that of the active therapy. This technique appeared to be successful in not having impact on symptoms related to the constipation. Thus, IFT resulted in improvement in all symptom domains of the PAC-SYM as opposed to sham stimulation. However, sham stimulation appeared to impact positively on pain on defaecation, but not after Bonferroni correction for multiple corrections. The tendency for improvement in pain might represent a residual analgesic effect from a current passing through skin and abdominal tissue, where the somato-visceral reflexes could possibly be induced, thereby modifying visceral function[241]. It is noted that the symptoms with a sensory component trended toward higher significance in the IFT group than other measures such as stool type or bleeding from the rectum (as assessed in the PAC-SYM). A study on sensation and sacral nerve stimulation in IBS found alleviation of painful stimuli, suggesting an effect on visceral afferent pathways[141]. Perhaps less painful sensations reduce anxiety, impacting on the gut-brain axis[3]. Rectal sensation is explored in the next chapter.

Thus, the overall impression of this technique of sham therapy was that it represents a successful and novel means of creating a control arm for studies in the use of interferential electrical stimulation. Medium or high frequency currents penetrate tissue easily and oscillate too rapidly to stimulate tissue it passes through[153]. The two slightly out-of-phase medium frequency currents (Samuel 2015) need to cross in order to create the low frequency therapeutic current, therefore, if these currents did not bisect, the therapeutic current is not created. The low placebo response in this study suggests that the sham method of stimulation is a valid placebo control. Other studies in adults have reported much higher responses in their placebo groups, which could be related to the fact questionnaires were

answered face to face with the researchers[185, 186]. Their placebo groups had no stimulation, and it is, therefore, possible that responder bias may have occurred. Our findings will facilitate future studies, as "sub-sensory or no stimulation" (as used previously) is likely a poor placebo, particularly when undertaking studies in the home environment due to issues of believability. However, more studies are needed to test this.

The use of IFT is generally well tolerated with few side effects, notably the main one reported in the literature being diarrhoea[139]. This did not occur in any of our participants apart from the participant who had gastroenteritis. Participants found it easy to use, and there were few problems with the machines themselves. Even though this technique is acknowledged as being safe, non-pharmacological and non-invasive, there were some safety measures that needed to be taken into consideration. For instance, it is not known what effects stimulation would have on a developing foetus, and it is contraindicated if the person has a cardiac pacemaker or other implanted electronic device. There is also the potential for thermal burns if there are metal plates and/or screws in the region.

While we had no formal means of measuring compliance, the high completion rate of a 2-week diary after 3 weeks of stimulation would suggest patient adherence to the routine. Six weeks of stimulation may have been appropriate for maximum compliance, but better responses may have occurred with longer use as seen in some pilot studies, including that reported in the Chapter 6. However, 3 months is possibly too long when conducting a randomised controlled trial. A protocol for the "CON-COUR" study currently underway has participants use the treatment at home for an hour a day for 8 weeks[241]. The 6-week time frame in which participants used the interferential stimulation may well have been too short. Other studies using home based treatment had participants using it for a minimum of 3 months[98, 188], but these were not RCTs.

The current study has several strengths. First, it studied a range of outcomes using validated measures to better assess the many aspects of chronic constipation. Secondly, the use of stimulation at home for one hour a day was of practical advantage and minimised the placebo effect of frequent visits if delivered at the hospital. Thirdly, the pragmatic approach allowing participants to use laxatives as required was closer to the 'real-world' and potentially avoided more withdrawals from the study had laxatives been banned. Finally, the use of a sham treatment that was probably indistinguishable from the IFT minimised potential bias from unequal placebo effects. However, the major limitation in this pilot study are the number of participants. An additional limitation is the lack of blinding of the study coordinator, which may possibly have had an inadvertent placebo effect on those in the actual therapy group despite minimising contact with all participants. It takes considerable acting skills to ensure totally benign actions in teaching both the actual and sham stimulation to participants.

7.4.1 Conclusions and future directions

Transabdominal interferential electrical stimulation is an effective and well tolerated non-pharmacological method of treating women with constipation. It has benefit in improving both symptoms associated with constipation and probably quality of life. While the study was limited by the number of participants, the results are highly encouraging and the technique warrants more comprehensive investigation. There remains limited understanding of potential mechanisms of action for interferential stimulation or for whom this treatment may benefit, but this will be explored in the next chapter.

CHAPTER 8: TRANSABDOMINAL INTERFERENTIAL ELECTRICAL STIMULATION IN WOMEN WITH CONSTIPATION: MECHANISMS OF ACTION AND PREDICTORS OF RESPONSE:

8.1 Background and aims:

Transabdominal interferential electrical stimulation appears to be effective in reducing symptoms of constipation though few studies address the mechanism of action. In the paediatric population, colonic transit time is reduced following at least 4 weeks of stimulation[152] and IFT was associated with an increase in propagating sequences on colonic manometry. However these studies were uncontrolled and retrospectively analysed[162]. Furthermore, a second study found there were anorectal manometric changes following IFT, comprising decreased sphincter pressure and decreased volume required to induce the recto-anal inhibitory reflex (RAIR). These changes were thought to result from an influence of the sacral nerves reflexes[180]. Despite this, there is still no clear understanding of the mechanisms of action of IFT.

This is not surprising, as there is also limited understanding of the mechanism of action of other neuromodulatory techniques, although more research has been conducted in this area. Animal studies of sacral nerve stimulation, for example, have found it to correct rectal sensory defects, but with limited impact on anorectal motor function[244]. Similar changes in rectal sensory function have been seen in humans[103, 141] although SNS appears to alter contractile patterns in the colon[245] without

necessarily changing the overall colonic transit. Based on the current literature, it has thus been proposed that neuromodulation may work via stimulation of either pelvic afferent pathways or via modulation of central processing[103]. It is possible that IFT acts in a similar way. Certainly, IFT subjectively improved the sense of an "urge to defaecate" in those children who previously noted an attenuated call to stool suggesting modulation of afferent function as a potential mechanism of action[152], although rectal sensory testing was not formally conducted. Response to IFT does appear to be durable post cessation of therapy suggesting that IFT may have neuroplastic effect on the enteric nervous system.

There are also few studies examining whether clinical indices predict response to neuromodulatory therapy. Given the changes seen in colonic transit time in paediatric studies, it is suspected that patients with slow transit constipation may particularly benefit from this therapy. Unfortunately, to date no studies have examined this adequately.

Hence, the aims were to perform an exploratory sub-study of the patients in the randomised controlled trial described in Chapter 7, in order to:

- explore the potential mechanisms of action of interferential stimulation; and
- assess clinical and physiological measures at baseline that may predict response to IFT.

8.2 Method

8.2.1 Participants

Recruitment and randomisation were detailed in Chapter 7. Recruitment for this sub-study was delayed by approximately 12 months due to unavailability of equipment. Prior to recruitment participants were given the participant information with detailed information on the tests. This sub-study was also optional for patients and some elected to participate in the clinical arm only. Consequently, only a subset of participants undertook physiological studies.

8.2.2 Protocol

Subjects underwent a radio-opaque marker colonic transit study and anorectal manometry prior to commencing either IFT or sham therapy and again within 4 weeks of completing the 6 weeks of treatment. Participants who withdrew prematurely did not have repeat testing. The results of the testing were blinded to the principal investigator and were analysed by both the principal investigator and the study coordinator individually after the participant had completed the study. Results therefore did not have any bearing on interactions with the participant during the study.

8.2.3 Physiological measures

8.2.3.1 Anorectal manometry

Anorectal manometry was performed as described in detail in Chapter 3 using the 3-D HDAM anorectal manometry system (Given Imaging). Participants attended alongside patients undergoing anorectal manometry on a Friday morning. The study doctor reiterated information about the procedure where a detailed description of the procedure was given and verbal consent gained even though signed consent to the study had already occurred prior. A digital rectal exam as performed

prior to insertion of the probe to ensure the rectum was empty where a Fleet enema was given if there was stool present that would impede the ability to perform the test.

Manometric data collected included:

- mean anal resting pressure
- maximal anal sphincter squeeze
- percentage of anal relaxation on attempted defaecation
- mean rectal pressure applied on attempted defaecation
- presence or absence of poor propulsion during attempted evacuation
- presence or absence of inappropriate pelvic floor or anal contraction during attempted evacuation
- presence or absence of an inappropriate relaxation (< 50%) of the anal sphincter during attempted evacuation

Rectal sensory status was examined using latex balloon distension via a continuous inflation of the balloon to assess sensation. This is described in Chapter 3.5.10. Rectal hyposensitivity was diagnosed if 2 or more sensory thresholds were higher than reference ranges (defined as per Li, 2013)[199]. Rectal hypersensitivity was determined by a maximum tolerated volume below 135 ml, as per Li, 2013. (Chapter 3.5.10.)

8.2.3.2 Colonic transit studies

A plain abdominal x-ray for the colon transit studies (as per Chapter 3.5.9) was taken 5 days after a capsule containing 20 biomarkers was swallowed. Participants were required to cease laxative use over the 5 days between taking the capsule and having the x-ray. If there were 5 or more biomarkers retained within the bowel as shown on the x-ray results were reported as slow transit colon, where

less than 5 biomarkers results were reported as normal transit colon. The majority of participants elected to have the x-ray done the same day as manometry for convenience.

8.2.4 Data analysis

As this was a pilot study no power calculations were computed. Results of anorectal manometry obtained at the end of the treatment period were compared with pre-study data. Groups were tested for normality and for parametric data a paired t test was used. For non-parametric data a Wilcoxon sign-rank test was used. Changes in anorectal manometry measures following treatment were compared between groups by Mann-Whitney U test. The proportion of participants who had been diagnosed with slow transit colon were identified and the proportion of those who normalised following treatment were compared between groups. (Fisher's exact test). Response rates were calculated in those patients who received active therapy and response was defined as those who achieved the primary outcome of more than 2 spontaneous bowel motions a week (as defined in Chapter 7). The proportion of responders were analysed by a Fisher's exact test. Statistical significance was determined by a P value ≤ 0.05.

8.3 **Results**:

8.3.1 Participants

Twenty-one participants underwent anorectal manometry and colonic transit time studies. Only 1 participant did not undertake physiological studies due to travel distance. Eleven received IFT and 10 received sham stimulation. Of the 11 patients who received active IFT, 7 were defined as clinical responders and 3, non-responders. Unfortunately, 1 participant in the IFT group did not return any clinical data (see Chapter 7) and only physiological results were available. This patient was excluded from the analysis of predictors of response. Five participants delayed commencing treatment after

initial testing, 2 for ill health/planned surgery, 3 for timing issues. Range of delay was from 1 month to 3 months. Their bowel symptoms did not change in the meantime. After the 6 weeks of treatment, 6 of 21 had a delay of 2 to 3 weeks before they could have the investigations. Participants tolerated the procedure well and there were no concerns reported. Only one participant required an enema to empty the rectum so the procedure could be performed.

8.3.2 Anorectal manometry

The groups were well matched for age, with the median age in the IFT group being 48 years and the sham group 35 years (P=0.2). There were no differences in baseline sphincter pressure or rectal sensory thresholds between the active treatment and sham treatment groups (Figures 8.1 and 8.2), but patients allocated to sham treatment had lower intra-rectal pressure during strain (P=0.007). As described in Chapter 7, there were no differences in clinical measures between the two groups at baseline.

Twelve patients had isolated slow transit constipation, 7 in the IFT group and 5 in the sham stimulation group. Seven patients had an isolated functional defaecation disorder, 4 in the IFT group and 3 in the sham group. One patient in the IFT group had both slow transit constipation and a functional defaecation disorder. Eleven patients had rectal hyposensitivity and 7 had rectal hypersensitivity.
Eight with rectal hyposensitivity were in the IFT group and none with rectal hypersensitivity. Three with rectal hyposensitivity were in the sham group as were 6 with rectal hypersensitivity. The effects of treatment on the classification of the patients is shown in Table 8.2. There were no trends for effects of either IFT or sham treatment.

After the 6-week stimulation period, there were no differences between the groups in the change of all manometric data measured. Furthermore, there was no significant change in all 3 rectal sensory thresholds. (Figure 8.3)

There was a significant drop in resting pressure in the IFT group following treatment (P=0.01) where there was no change in the sham group. There was no difference in either group for maximum squeeze or % anal relaxation. However, there was a significant difference in the sham group with increased intra-rectal pressure (P=0.04) Table 8.1.

Table 8.1 Manometric values in the IFT group and sham treatment group after 6 weeks of treatment. Values shown are median (IQR). Changes in paired data were normally distributed and compared using a paired t test

	IFT pre N=11	IFT post	P value	Sham pre N=10	Sham post	P value
Resting pressure mm Hg	77 (65-84)	63 (55-73)	**0.01**	80 (63-99)	81 (63-91	0.5
Maximal squeeze mm Hg	160 (115-187)	176(151-196)	0.7	187 (133-229)	179 (129-234)	0.4
Anal relaxation percentage	31 (18-53)	47 (24-59)	0.1	35 (23-47)	35 (20-52)	0.2
Intra-rectal pressure mm Hg	61 (43-108)	56 (32-87)	0.6	29 (6-50)	71 (24-94)	**0.04**

Table 8.2 Normalisation in anorectal manometry data, rectal sensation and colon transit times following 6 weeks of treatment

	IFT group **N=11**	**Sham group** **N=10**	**P value** Fisher's exact
Normalisation of colonic transit time	1/7 (14%)	0/5 (0%)	>0.9
Normalisation of results in manometry	2/4 (50%)	1/3 (33%)	>0.9
Normalisation of both transit time and manometric data	1 /2 (50%)	0/1 (0%)	>0.9
Normalisation of rectal hyposensitivity	4/8 (50%)	0/3 (0%)	0.2
Normalisation of rectal hypersensitivity	0/0 (0%)	2/4 (50%)	>0.9

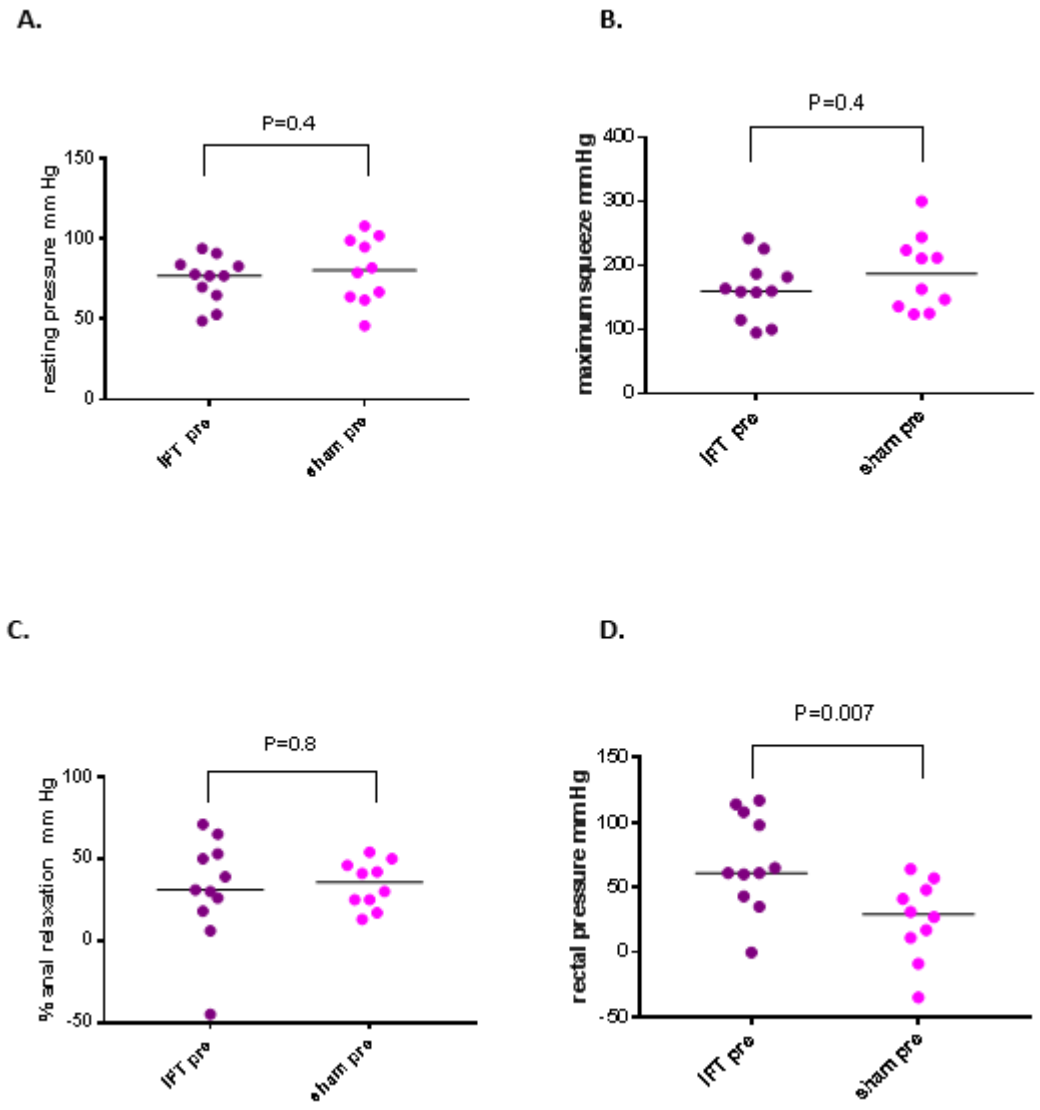

Figure 8.1 Anorectal manometry measures pre IFT in both groups for A) resting pressure; B) maximal squeeze; C) percentage of anal relaxation; and D) Intra-rectal pressure on push manoeuvre. The horizontal bars represents median value. Statistical comparisons were made using a Mann Whitney U test

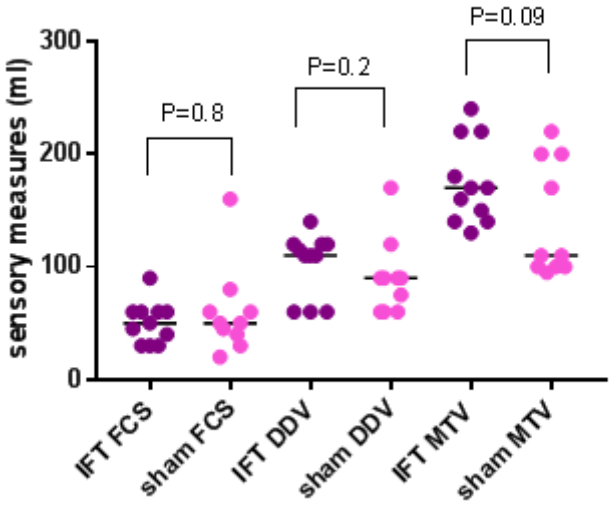

Figure 8.2 Rectal sensory threshold measurements in ml for baseline in both interferential therapy (IFT) and sham groups in first constant sensation (FCS); defaecatory desire volume (DDV) and maximum tolerated volume (MTV). Statistical comparisons were made using a Mann Whitney U test

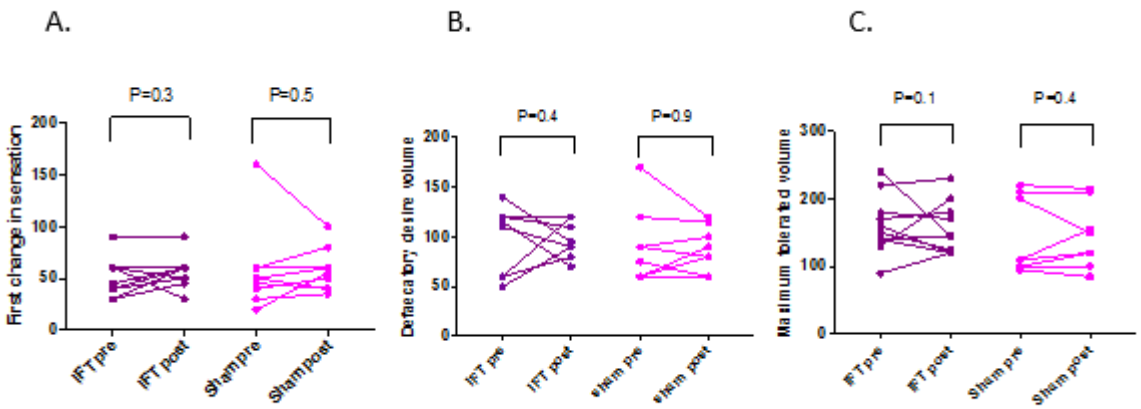

Figure 8.3 Rectal sensory levels (ml) before and after both IFT or sham in both groups. A = FCS; B = DDV; C = MTV. Statistical comparisons were made using a paired t test.

8.3.3 Colon transit time

There were 7 participants in the IFT group and 5 in the sham group who were identified with slow colonic transit. Only 1 participant in the IFT group normalised transit time with a reduction of markers from 16 pre treatment to 3 post treatment (Table 8.2). None in the sham stimulation group experienced a normalisation of transit time.

8.3.4 Predictors of response

Of the 10 participants in the IFT group who underwent anorectal physiology and colon transit studies, 7 (70%) were defined as responders according to the primary endpoint of more than 2 spontaneous bowel movements per week. There was no signal that underlying physiology (STC vs. FDD) predicted response to therapy. (Table 8.3). No manometric, sensory or clinical values that predicted response to interferential therapy were identified (Tables 8.4 & 8.5)

Table 8.3 Baseline constipation subtype stratified by response (spontaneous bowel movements > 2 per week at 6 weeks) following 6 weeks of interferential therapy.(Fisher's exact test)

	Responders N=7	**Non-responders N=3**	**P value**
Isolated functional defaecation disorder	2 (28%)	1 (33%)	>0.9
Isolated slow transit constipation	4 (57%)	3 (100%)	0.4
Both slow transit and functional defecation disorder	1 (14%)	0 (0%)	>0.9

Table 8.4 Baseline clinical features stratified by response (spontaneous bowel movements > 2 per week at 6 weeks) following 6 weeks of interferential therapy (Fishers exact test)

	Responders (N = 7)	**Non responders (N = 3)**	**P value**
Age – median (IQR)	51 (32-66)	36 (32-49)	0.3**
Discomfort	4 (57%)	2 (66%)	0.5
Abdominal pain	1 (14%)	1 (33%)	>0.9
Bloating	5 (71%)	1 (33%)	0.5
Cramping	1 (14%)	0	>0.9
Pain on defaecation	3 (42%)	2 (66%)	>0.9
Burning in rectum	2 (28%)	0	>0.9
Bleeding from rectum	0	1 (33%)	0.3
Incomplete evacuation	5 (71%)	3 (100%)	>0.9
Hard stools	2 (28%)	2 (66%)	0.5
Small stools	3 (42%)	1 (33%)	>0.9
Straining	3 (42%)	3 (100%)	0.2
False alarm	3 (42)	0	0.4

** Mann Whitney U test

Table 8.5 Baseline manometric features stratified by response (spontaneous bowel movements > 2 per week at 6 weeks) following 6 weeks of interferential therapy. All results are shown as median (IQR). No statistically significant differences were observed between the groups (Mann Whitney U test)

	Responders N = 7	Non responders N = 3	P value
First constant sensation	45 (30-60)	60 (40-60)	0.5
Defaecatory desire volume	110 (60-120)	110 (110-120)	0.9
Maximal tolerated volume	150 (140-220)	180 (170-220)	0.4
Resting pressure	77 (53-91)	78 (70-84)	0.8
Maximum squeeze pressure	159 (115-226)	163 (103-188)	>0.9
Anal relaxation %	39 (26-53)	30 (-45-71)	0.8
Rectal pressure	60 (35-61)	108 (98-114)	0.1

8.4 Discussion

Interferential therapy has now increasing evidence of efficacy in improving bowel habits in patients who are chronically constipated, as exemplified by the placebo-controlled study in Chapter 7. A key question is just how the technique of IFT exerts its effects. The current study was exploratory in nature and controlled, assuming the sham treatment was truly placebo. There was no signal that IFT was associated with normalisation of colonic transit. However, alterations of anorectal physiological measurements were observed. Anal resting pressure was reduced in the IFT group and intrarectal pressure on push manoeuvre increased in the sham group. Response of symptoms to therapy was not associated with any pattern of anorectal manometry or transit, either prior to therapy or associated with therapy.

In this study, only 1 participant with slow colonic transit during the baseline period normalised colon transit time and this occurred in association with IFT. As applied, the method used to measure colonic transit is not sensitive enough to detect change in colonic movement including segmental variation, but it was selected with a higher number of participants in mind as it is simple and accessible. More than 5 radio-opaque markers retained anywhere in the colon after 5 days is a relatively crude method of suggesting a slow transit, reporting of results was binary, either the participant had retained markers, or they did not. Therefore, with small numbers, this was not the ideal method of investigation. It is possible that changes did occur, but we were not able to capture this. Previously, in children, a reduced colon transit time has been found[176, 181] where there was an increase in colonic propagating sequences (Clarke 09). Furthermore, a small pilot study in adults with slow transit constipation found a median decrease of 5 hours in transit time[98]. Studies that have shown a change in colon transit times did so using nuclear transit studies or 24 hour ambulatory manometry[81, 98, 162]. Such tests are more sensitive but involve much higher doses of ionising radiation, time and effort, or

invasion than radio-opaque marker studies. For future studies though, nuclear transit studies or wireless motility capsule measures may be more appropriate.

In studies that have shown a reduction in transit time participants used IFT daily at home for a longer duration, from 3 to 6 months[98, 178]. It is thus possible that the shorter duration of stimulation (6 weeks) may have contributed to the lack of discernible response. Particularly as it has been suggested that IFT may have a neuroplastic effect rather than a direct effect on muscle[152]. Potentially this could result in a slower onset of action[164], but it is difficult to reconcile this with the clinical benefits identified in Chapter 7. A more likely explanation is that the colonic radio-opaque marker studies were not sensitive enough to detect change.

Findings from anorectal manometry include a significant reduction in anal resting pressure following treatment in the IFT group (P=0.01). This finding is in keeping with a study on IFT in children with myelomeningocele, which showed an improvement in anal sphincter pressure and the rectoanal inhibitory reflex[180]. The authors suggested that IFT can have an effect on sacral reflexes controlling bowel function where it is possible that the reduced RAIR volume may represent a change in rectal sensation. The 2 groups were matched for this measure. However, the 2 groups were not matched in some anorectal manometry measures. While there was no significant difference in age, the median age for the sham group was more than 10 years younger than the IFT group. Pre-intervention, there were no differences in median rectal sensory values, anal resting pressure, anal squeeze pressure or percentage of anal relaxation on push manoeuvre, but there was a significant difference between groups for intra-rectal pressure on the push manoeuvre (P=0.007). This may have some bearing on findings after intervention where, in the sham group, there was a significant increase of intra-rectal pressure on the push manoeuvre (P=0.04). It was unfortunate that randomisation could not account for equality in the diverse manometric measures. This is highlighted by the failure of intra-rectal

pressure to being no different between groups, where the not only was the group younger, but had a lower rectal pressure, usually seen in an older population[105].

The use of 3-D HDAM is relatively new and reported normal values differ across studies[105, 199, 246]. Reproducibility of manometric results is as yet well established and various factors may influence the results. First, inconsistency of instructions to patients, particularly if there is a different operator, may be an issue, but every attempt was made in the current study to have the same person perform the testing as much as possible. Secondly, this novel means of assessment still lacks protocol standardisation[246]. However, one operating protocol was strictly adhered to in the present study. Thirdly, patient factors such as anxiety or difficulty following instructions may have played a part in variance of results. For example, the younger people in the sham stimulation group may have grasped the concept of that particular manoeuvre more easily than the slightly older group. The change in resting pressure is likely to be a valid finding as this is done with the patient quiet and still for 2 minutes before the recording is taken with no input from the patient whatsoever. All other manoeuvres require patient involvement apart from the RAIR which is a reflex test only.

Individually there were small changes in patterns of dyssynergia identified in both groups. We found a change to normalisation of sensory values in 50% of those identified with rectal hyposensitivity in the IFT group, and none in the sham group. It was the reverse for those with rectal hypersensitivity, where 50% in the sham group improved. As there were no participants in the IFT group that had been identified with rectal hypersensitivity, a true comparison cannot be made. However, this result may represent a placebo response or be related to less anxiety at the second visit, which may have affected their sensory response. The fact that both groups tended to normalise also raise the possibility that the changes over time represented the phenomenon of regression to the mean.

Clues to the clinical significance of the changes observed might derive from comparison of responders with non-responders. There were no clear links in anorectal measurements or colon transit time to those in the IFT group who had a clinical response to treatment. Reduction in resting pressure was observed in only 3 of the responders, but none of them had a dyssynergic pattern to defaecation, nor did they exhibit an abnormal rectal sensitivity. Hence, the findings in this small cohort provided no positive support for clinical significance in the changes observed in specific manometric indices.

The present study has several limitations. First was the likely insensitivity of the markers used, particularly the colonic transit methodology, to show subtle changes. Secondly, it is possible that the timing of the post-study testing impacted on the ability to detect further physiological change. Although we aimed to perform anorectal manometry and the transit study as close to ceasing use of treatment as possible, due to both clinical and participant availability constraints on several occasions, it proved difficult to time it precisely. Thirdly, and probably most importantly, the ability for the study to detect a difference in physiological measures was impacted by the small sample size of this study. There were no signals detected that would help determine the numbers needed for a larger study though the most obvious choice would be rectal sensation as 50% of those in the IFT group did have a change in sensation. As the two groups were not matched in rectal sensation due to this being a sub study it is not possible to do a power calculation. The groups were not matched for rectal pressure on push manoeuvre either. Much larger groups are needed to control for this. Further open label studies with greater numbers of participants will be needed to adequately answer this question.

8.4.1 Conclusion.

This exploratory, hypothesis-generating study was conducted in a subgroup of participants in the randomised controlled trial in Chapter 7. There were mixed findings with changes in resting pressure in the IFT group, and an increase in rectal pressure in the sham group following 6 weeks of IFT.

Normalisation of colonic transit was not observed in association with improved symptoms, although more subtle changes were not assessed. Findings of a reduced anal resting pressure following IFT is supported in the literature where it is suggested IFT may have a neuroplastic effect[164, 180]. However, clinical significance of this isolated finding was not apparent. Further studies are needed to further explore the meaning of this change. That clear explanations of the mode of action of IFT in this to this exploratory study were not identified encourage limitations of the study in the methods of assessing colonic transit, the timing of assessment of the IFT-related effects and the sample size will need to be addressed in future studies.

CHAPTER 9: GENERAL DISCUSSION

Functional GI disorders are complex and often share symptoms with other concurrent conditions that require unique management strategies. In recent years, there have been changes in management approaches that have seen greater involvement of allied health specialities, particularly dietitians and psychologists. The original work presented in this thesis has explored the role of the specialist nurse in not only diagnosis, but also treatment methods for gastrointestinal dysmotility disorders. Within this thesis, a variety of aspects of the potential role of the nurse is presented. These have included: (1) a protocol-driven nurse-led clinic in identification and management of IBS and comorbid conditions; 2) effective nurse-led implementation of a low FODMAP diet in patients with IBS; 3) an evidence-based care plan for ward nurses to use to manage and prevent constipation; and 4) in research, the evaluation of the efficacy of a novel, non-pharmacological intervention for the management of refractory gastrointestinal dysmotility disorders.

A key theme that has recurred throughout this thesis is that FGID, in particular IBS and constipation, have historically not been easily identified and/or managed in the current healthcare model. Throughout the literature there are discussions around the diagnosis of the various FGID, the necessity, or not of detailed investigations, and the exploration of predominantly medical/pharmacological management strategies[23, 27, 94]. What is clear is that, in the community, IBS is not well identified or managed[30, 201, 247], that management of acute onset constipation related to hospitalisation is reactive rather than proactive[82], and that there is a need for an alternative, non-pharmacological treatment strategy for functional dysmotility disorders[248]. This thesis has, therefore, focused on strategies to improve the ways we can structure our model of care in FGID outpatient

clinics, especially with respect to key roles for nurse management within the assessment/treatment paradigms.

9.1 The principle of multi-disciplinary management in patients with FGID

Within Chapter 4, knowledge gaps in the identification and management of FGID were identified. The vast majority of referrals of patients with presumed FGID to a private nurse-led service in New Zealand were from local general practitioners. The number of alternate diagnoses identified at the first contact with the nurse specialist highlighted deficiencies in the current diagnostic process and, as such, without quality diagnosis, optimal management and outcomes of patients will be compromised. A question does need to be asked. Does such diagnosis need to be made by a medical practitioner? There are diagnostic tools available such as the Rome criteria for the identification of the different functional disorders and these, in the hands of an appropriately-trained healthcare practitioner, can enable accurate diagnosis[53].

Anecdotal comments from GPs in letters of request to the nurse-led service in New Zealand, and from junior doctors in a major teaching hospital are that FGID are not part of the curriculum in medical school and that they do not know how to adequately manage such complaints. Doctors have reported they do not know what causes IBS, for instance, and were unfamiliar with diagnostic criteria[201, 247]. It is, therefore, not surprising that the quality of referrals left much to be desired. There has historically been poor understanding among primary health care practitioners about the nature of FGID. For example, a common bias is that IBS is a psychosomatic disorder and there is nothing seriously wrong; the patient just needs to go home and learn to live with it[201]. This leads to a frequent disconnect between patient and doctor expectation where all too often the patient does not accept the doctor's

diagnosis[249]. Patient complaints suggesting that their health care practitioner does not listen, is not helpful, and is quick to reach for the prescription pad are reasonably common[250]. The structure of general practice is one of rapid patient turnover, which is not conducive for optimal communication. Over a third of primary care physicians feel IBS patients need to see a gastroenterologist[247].

However, commonly, patients may feel threatened by medical specialists, in part because of the inferred power imbalance inherent in the doctor-patient relationship[250, 251]. Hence, a high number of patients attend busy gastroenterology clinics in tertiary care where they are frequently over-investigated and mostly managed medically[250]. Gastroenterologists, who often see these patients as challenging, can hold negative attitudes towards such individuals, describing them as “heart sink” patients, perceiving them to be not as sick as those with organic disease, but taking up more consult time[252]. It is not surprising that a high number of patients are disheartened by the medical community and turn to complementary and alternative medicines (CAM) often as a last resort[251], and frequently at great expense. Frustration over perceived inadequate explanations of aetiopathological mechanisms underlying FGIDs by the health care provider is frequently expressed[250]. As a result, some patients give up and try to manage their symptoms themselves. An observation was made that less than a third of patients were satisfied with the management plan when given by their doctor[202] where over 50% IBS patients have turned to CAM[251]. In the age of the internet, this places patients at risk of physical and economic harm either from unproven therapies or expensive placebos. Self-management is risky, particularly as food is commonly identified as a trigger of symptoms, and the number of diets that are available on the internet put people at risk of developing both orthorexia and malnutrition. For many there is not easy access to appropriate care.

Functional gut disorders can be competently identified and managed by experienced nurses when not complicated by complex co-morbidities[202]. Time constraints can be offset in the setting of the experienced nurse consultation[202], where generally time is quintessential as is validation and

education. The combination of holistic nursing skills, knowledge of both the patient and their condition, coupled with consultation and physical assessment skills are seen to generate an effective trust relationship[253] where patients often find nurses more accessible and may disclose pertinent information more readily to nurses[46]. Time taken to educate patients contributes to the patient's ability to begin to take ownership of strategies needed to relieve symptoms[46].

There is corroborating evidence in the literature for the findings in this thesis that the use of a structured protocol with validated tools used by nurses is at least as effective as a medical model in the management of chronic disease[209]. Experienced nurses have been seen to improve the provision in healthcare in specific population groups[253] where patient education and therapeutic strategies are key components in nurse consultations. This was exemplified in Chapter 4, by the application of the structured protocol leading to either IBS or alternate diagnoses, and consequent validation, education around IBS, and provision of management strategies.

Other service providers such as dietitians, psychologists, hypnotherapists and physiotherapists contribute different strategies that assist patients with FGID in symptom control[202]. The ideal is to individualise management when there are several potential (and different) therapeutic strategies within a multi-disciplinary team environment. However, access to such services can be difficult with few specialised FGID clinics in existence. The waitlist for these services is long; for example, it may take over 18 months to see the doctor at one large public hospital Melbourne FGID clinic (Dr Rebecca Burgell, personal communication). A recent review of models of care found that a nurse-led model is effective and economical, with high patient satisfaction and improved quality of life[248]. However, further research is needed in this area. With the growing understanding of the nature of FGID and of effective management strategies, the need for an integrated team approach with the use of both a nurse-led and allied health team approach is more apparent.

9.2 Specific roles for the nurse-specialist

Within this thesis, a variety of nurse-led approaches have been evaluated and/or explored, from which thoughts on how to better manage patients with FGID have arisen. In the case of ambulatory care in a specialised clinic setting, the application of a nurse-led protocol, stemming from learnings outlined in Chapter 4, has now been developed with the model of care focussed on allied health. Thus, an experienced nurse triages patients and steers them to the appropriate resource, so that those who do not need medical intervention are managed more rapidly, and the waitlist for specialised management strategies is much reduced, appointments with the doctor reserved for those with whom red flags have been raised or clear alternate diagnoses suggested. Such a model will no doubt lead to some patients feeling inadequately managed until they have seen the doctor. A recent study examining an algorithm-based approach to screening and management strategies of referred patients found this method to be moderately acceptable. A number of patients still did not believe the diagnosis and wanted specialist medical management[248]. Nevertheless, if the protocol is well designed and followed, reassurance is there for the patient that they are under team care, which should include doctors who are informed of patient problems and progress.

The use of a structured protocol in both Chapters 4 and 5 sits well within the literature that is available where a nurse is able to manage a patient's condition in an expanded role under the guidelines of the relevant protocol[254]. Results from such practice have shown a strongly positive effect on the management of patients with a variety of chronic diseases, with improved biophysical outcomes and reduced ED or hospital admissions. Within Chapter 4, the use of a protocol assisted in the identification of IBS, comorbid conditions that shared the same symptoms and alternate diagnoses that required referral on to the appropriate clinician. This protocol was aimed at the level of a clinical nurse specialist. Within Chapter 5, the protocol, or evidence-based care plan as it was known in that particular study was aimed at a more general group of nurses working in the ward situation. In this

Chapter, a standardised bowel care plan used by nurses to prevent onset of constipation in a high-risk in-patient setting was designed to empower nurses to confidently make decisions in implementing appropriate management. While there is limited literature on this topic, the majority of those that do exist had findings of improved nurse knowledge and better patient outcomes, similar to our findings[189, 226, 228, 229]. Though structured protocols used by nurses improve patient outcomes, (Martinez-Gonzalez) they tend to be specific for the setting in which they are applied; for instance, the structured bowel management plan described in another rehabilitation setting[226] was not transferable to the ABIU population described in Chapter 5. As a result, a protocol was developed to cater to the targeted population group some of whom had unique requirements. It also needed to be simple and easily applied. Our protocol was directive, in contrast to the protocol for management of constipation in a geriatric setting which used the words "consider rescue laxative" or "consider maintenance laxative". (Klein 2016) This does not give the nurse a direct action. To feel safe and confident in what they do, particularly in the ward setting where there is a range of expertise, a care plan or protocol must be able to be used by all nurses.

The number of nurse-led protocols available vary from very simple, to complex flow diagrams that take some time to decipher[189, 209, 226, 229]. There is a paucity of information around a validated protocol for nurse-initiated interventions that are transferable to the gastrointestinal setting. Nurse-led protocols need to be clear, and designed to protect both the patient and the nurse. As identified in Chapter 4 and also seen in a recent study by Linedale[248] (2017), a number of patients referred to a nurse-led service with presumed IBS were subsequently found to have an organic alternate diagnosis[46, 248]. For this kind of protocol, there must be included a detailed questionnaire that captures any potential red flag(s) and, as such going forward with a new design in a functional gut clinic, there should be detailed questionnaires that include psychological and nutritional indices as well as symptoms and demographics so that patients needing specialist medical care can be identified early.

It is not known how many nurses practice at an advanced level, though there is evidence of nurse-led clinics in the literature, generally in response to long wait lists for patients to be seen by a medical practitioner in chronic disease management[255]. The role of an advanced practice nurse or nurse consultant in Australia is not clear, with poor delineation of scope[256], It is very much an individual's desire to expand their practice and look outside the square as there is little incentive or funding from employers to achieve the next level[257]. There is little support or understanding of the nurse working in a more advanced role in Australia[258]. It is experience and education that create an advanced practice nurse, and experience that the nurse provides can cross typical medical and other allied health borders. Yet, it is the ability to function at a higher level with experience that defines a nurse specialist/consultant/advanced practitioner[258]. It is up to the individual nurse however to prove her/his worth[259].

A clear example of crossing boundaries is seen in Chapter 4 in both the use of advanced health assessment skills, a skill historically held closely to the chest by the medical fraternity[259], and in the use of dietary recommendations, in particular the low FODMAP diet. While the ideal is its administration by a dietitian, practically that is not always possible. The nurse practising at an advanced level seeks education in areas of deficit in order to bring a holistic approach to patient management, which was what underpinned practice as seen in Chapter 4. The "excitement" that dietitians and gastroenterologists experienced in the advent of the low FODMAP diet[260] also grabbed the attention of the nurse working with patients with IBS. As access to an appropriately trained dietitian was not always practical, the nurse in Chapter 4 attended courses held for dietitians on the use of the low FODMAP diet and liaised frequently with a dietitian to whom she was able to refer a few patients.

The discovery that the low FODMAP diet was helping women with endometriosis was corroborated by anecdotal comments from dietitians yet to date there has been no other study on the efficacy of the low FODMAP diet in this situation to support this. The link between IBS and endometriosis including sharing visceral hypersensitivity has been made[37, 38, 261], but this therapeutic connection that appears so obvious has not been made. Therefore, it is important that further study into the role of the low FODMAP diet in relieving bowel symptoms in women with endometriosis is undertaken.

9.3 Novel nurse led strategies in functional GI disorders

Another strategy that can be administered by a nurse or other allied health professional is transabdominal electrical interferential stimulation. This was explored in Chapter 6 in the treatment of functional dysmotility disorders refractory to the usual management strategies such as dietary modification, lifestyle changes and pharmacotherapies. Given the positive results in open-label use, IFT was the focus of a clinical RCT examining efficacy, mechanism of action and predictors of response. IFT is considered safe and without major contraindications other than pregnancy or an implanted electrical device (where there is no information of safety). It can be applied without medical involvement, and can be instituted by a specialist nurse or physiotherapist[166, 175]. Our study found that participants were able to significantly reduce their laxative use, which no doubt also contributed to their improved quality of life. This is in line with the paediatric literature where children with constipation also responded well to IFT, particularly after using it for 3 months at home[178].

There is still little exploration of this novel means of treating constipation with only a handful of studies in adults[98, 184, 186], and a few more in children, mostly arising from the same institutions[152, 179, 180]. Given the positive results of Chapters 6 and 7, this area warrants wider application, which would benefit from far more research in order to make this more available as a treatment for many who are refractory to usual management strategies.

Despite an increasing number of studies showing efficacy of IFT in patients with FGID, little is actually known as to how it works. It was thus disappointing that the pilot studies undertaken in Chapter 8 failed to detect significant physiological changes following IFT. Although the negative findings may be related to low numbers of participants, the length of time in which the participants used the stimulator and the perhaps crude method of measuring colon transit times, there was no baseline clinical or manometric findings that predicted response to IFT. The two groups were not well matched physiologically, which would have confounded any potential findings. As there have been some findings suggestive of a neuroplastic effect in other studies[162, 180] much larger, well planned studies are needed to replicate such findings.

Observations in the case series described in Chapter 6 suggested that the cause of motility disturbance might help predict who is more likely to respond. Thus, those with a neuropathic cause of their upper GI dysmotility responded better to IFT than those with an idiopathic cause. This finding is reflected in some studies on gastric electrical stimulation (GES) where those with diabetic gastroparesis were the more responsive in both improved symptoms and in gastric emptying[15]. This was also reported in another study where those who had a major depletion of ICC or were opioid dependent patients did not do well with GES, as opposed to patients with diabetic gastroparesis[144]. Interestingly it was found in a study using a surgically-implanted means of neuromodulation for weight loss, that, in diabetic patients, there was regained glycaemic control rather than weight loss, suggesting a possible but unexplained metabolic action[133]. Therefore, we have no real understanding as to how neuromodulation in any form actually works. As with GES, there have not been sufficient studies conducted in IFT yet to know if this is an alternative therapy for gastroparesis. Given the positive findings of IFT in gastroparesis described in Chapter 6 that appear to be in line with the literature, this is an important area of future research. A pilot study implementing IFT comparing patients with a

neuropathic cause of gastroparesis vs idiopathic gastroparesis may be a step into predicting who may respond better to IFT. Perhaps monitoring blood glucose levels should be a part of the protocol.

The economic burden of FGID, not specifically studied in this thesis, is an important issue to consider. The current medical model of care is expensive. Patients with IBS-C incurred double the annual healthcare costs in comparison with matched controls[262], mostly from doctor visits and outpatient services. Economic benefits may arise for patients using the IFT method of treating dysmotility disorders, in particular constipation. It has been estimated that sacral nerve stimulation for IBS, for instance, costs around UK £25,000[263] whereas the transcutaneous method of stimulation is very cheap in comparison with a single purchase estimated at around AUS $450. This is cheaper than the annual amount spent by many on CAM supplements. Unfortunately, likely cost of ongoing medications including rescue laxatives carry an accumulative financial burden. Hence, it remains to be seen whether IFT is a realistic, viable alternative.

9.4 Conclusion

This thesis reports on novel means of identifying and managing a variety of functional gut disorders and associated comorbidities via several strategies. The use of structured protocols and novel interventions involving nurses and allied health are able to be an efficient means of managing patients with stable functional disorders, while identifying those who truly need medical assistance. This has the ability to reduce waitlist times, take over management from already overstretched medical resources, and improve patient symptoms and quality of life. Not only can diagnostic pathways be effectively followed, but therapies can be delivered by nurse-specialists trained in relevant techniques. Examples of the impact that can be made in patient outcomes explored in the thesis include first, nurse-delivered dietary advice as exemplified in the high response rates of the low FODMAP diet in patients with IBS and endometriosis. Secondly, the benefits to patients and to nursing staff were clear

when an evidence-based bowel management plan to identify and pro-actively manage constipation in the hospitalised patient were evident. Thirdly, the application of the novel, cheap and remarkably safe and well tolerated technique of trans-abdominal interferential electrical stimulation, which was effective in reducing symptoms of constipation and possibly gastroparesis, with concomitant reduction of medication use. Thus, overall, this thesis has shown that there is a far greater role for nurses in the identification and management of functional gastrointestinal disorders, with the ability to change the paradigms of management, traditionally the realm of the medical profession. In the wider picture of healthcare, this has greater implications overall and can be translated into disease-specific models of care by nurses in the management of other chronic illnesses.

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LIST OF APPENDICES

APPENDIX 1.

Constipation impact on nursing questionnaire

Study ID number _____ ☐ Pre care plan ☐ Post care plan

Q1. Does your ward have a bowel management plan?

No ☐ I'm not sure ☐ Yes ☐

Q2. How often should patients have their bowel function checked?

Every shift ☐ daily ☐ every 2nd day ☐ weekly ☐

Q3. How familiar are you with the Bristol Stool Scale? *(Place a mark on the line to show where you think your response lies)*

Never heard of it Know it well

_____

Q4. How does constipation in patients impact on your workload?

Very little Too much of my time

_____

Q5. What is your perception of how constipation impacts on your patients' quality of life?

Not at all Severe impact

_____

Q6. How confident do you feel in managing these patients' bowel symptoms?

Not at all confident Very confident

_____

APPENDIX 2:

FOCUS GROUP QUESTIONS

1. How would you define constipation?

2. What is current practice when a patient is found to be constipated?

3. How big a problem do you think constipation is among inpatients?

4. What challenges/impediments are there that may impact on management of constipation in the ward?

5. How could we do it better?

APPENDIX 3. Gastroparesis GCSI questionnaire

Name:_____

□ Pre stimulation □ Post stimulation

Over the last week how severely have you been affected by the following symptoms:

1. Nausea

□ None □ very mild □mild □ moderate □ severe □ very severe

2. Retching

□ None □ very mild □mild □ moderate □ severe □ very severe

3. Vomiting

□ None □ very mild □mild □ moderate □ severe □ very severe

4. Stomach fullness

□ None □ very mild □mild □ moderate □ severe □ very severe

5. Not able to finish a normal-sized meal

□ None □ very mild □mild □ moderate □ severe □ very severe

6. Feel excessively full after meals

□ None □ very mild □mild □ moderate □ severe □ very severe

7. Loss of appetite

□ None □ very mild □mild □ moderate □ severe □ very severe

8. Bloating

□ None □ very mild □mild □ moderate □ severe □ very severe

9. Belly visibly larger

□ None □ very mild □mild □ moderate □ severe □ very severe

APPENDIX 4: **SF-12 General quality of life**

1. **How would you describe your health at present?**
   - 0 ☐ Very good
   - 1 ☐ Good
   - 2 ☐ Fair
   - 3 ☐ Poor
   - 4 ☐ Very poor

2. **Overall, to what extent do your symptoms interfere with your life?**
   - 0 ☐ Not at all
   - 1 ☐ A little bit
   - 2 ☐ Moderately
   - 3 ☐ Quite a bit
   - 4 ☐ A lot

3. **To what extent do your symptoms affect your ability to perform daily tasks (e.g. dressing, shopping, cleaning etc)?**
   - 0 ☐ Not at all
   - 1 ☐ A little bit
   - 2 ☐ Moderately
   - 3 ☐ Quite a bit
   - 4 ☐ A lot

4. **To what extent do your symptoms affect your ability to perform physical tasks (e.g. lifting, walking, running or sport etc.)?**

   0 ☐ Not at all

   1 ☐ A little bit

   2 ☐ Moderately

   3 ☐ Quite a bit

   4 ☐ A lot

5. **To what extent do your symptoms interfere with your social activities (e.g. visiting friends, eating out, entertainment)?**

   0 ☐ Not at all

   1 ☐ A little bit

   2 ☐ Moderately

   3 ☐ Quite a bit

   4 ☐ A lot

6. **To what extent do your symptoms interfere with your work?**

   0 ☐ Not at all

   1 ☐ A little bit

   2 ☐ Moderately

   3 ☐ Quite a bit

   4 ☐ A lot

7. **Approximately how many days have you needed to take off work, directly as a result of your symptoms in the last year?**

   0 ☐ Not applicable

   1 ☐ 0-4 days

   2 ☐ 5-9 days

   3 ☐ 10-14 days

   4 ☐ 15-19 days

   5 ☐ 20 days or more

8. **To what extent do your stomach problems affect your relationship with your partner?**

   0 ☐ Not applicable

   1 ☐ Not at all

   2 ☐ A little bit

   3 ☐ Moderately

   4 ☐ Quite a bit

   5 ☐ A lot

9. **To what extent do your stomach problems affect your sex life?**

   0 ☐ Not applicable

   1 ☐ Not at all

   2 ☐ A little bit

   3 ☐ Moderately

   4 ☐ Quite a bit

   5 ☐ A lot

10. Do your stomach problems make you feel depressed/feel bad about yourself?

0 ☐ Not at all

1 ☐ A little bit

2 ☐ Moderately

3 ☐ Quite a bit

4 ☐ A lot

11. Do your stomach problems make you feel worn out/tired?

0 ☐ Not at all

1 ☐ A little bit

2 ☐ Moderately

3 ☐ Quite a bit

4 ☐ A lot

12. Do your stomach problems make you feel anxious or nervous?

0 ☐ Not at all

1 ☐ A little bit

2 ☐ Moderately

3 ☐ Quite a bit

4 ☐ A lot

APPENDIX 5. PAC-SYM ©

PATIENT ASSESSMENT OF CONSTIPATION

This questionnaire asks you about your constipation symptoms in the **past 2 weeks**. Answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

For each symptom below, please indicate **how severe** your symptoms have been during the **past 2 weeks**. If you have not had the symptom during the past 2 weeks, tick 0. If the symptom seemed mild, tick 1. If the symptom seemed moderate, tick 2. If the symptom seemed severe, tick 3. If the symptom seemed very severe, tick 4. Please be sure to answer every question.

How severe have each of these symptoms been in the past 2 weeks?	**Absent 0**	**Mild 1**	**Moderate 2**	**Severe 3**	**Very severe 4**
1. discomfort in your stomach	☐	☐	☐	☐	☐
2. pain in your stomach	☐	☐	☐	☐	☐
3. bloating in your stomach	☐	☐	☐	☐	☐
4. stomach cramps	☐	☐	☐	☐	☐
5. painful bowel movements	☐	☐	☐	☐	☐
6. rectal burning during or after a bowel movement	☐	☐	☐	☐	☐
7. rectal bleeding or tearing during or after a bowel movement	☐	☐	☐	☐	☐
8. incomplete bowel movement, as though you didn't "finish"	☐	☐	☐	☐	☐
9. stools that were too hard	☐	☐	☐	☐	☐
10. stools that were too small	☐	☐	☐	☐	☐
11. straining or squeezing to try to pass stools	☐	☐	☐	☐	☐
12. feeling like you had to pass a stool but you couldn't (false alarm)	☐	☐	☐	☐	☐

English (UK) PAC-SYM Version 2.0-S (12-item, Standard version)

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APPENDIX 6.

SYMPTOM VISUAL ANALOGUE SCALE

How severe have your bowel symptoms been over the last 2 weeks? *(please make a mark on the line that represents your experience)*

No symptoms Very severe

I_____I

APPENDIX 7. PAC-QOL

PATIENT ASSESSMENT OF CONSTIPATION ©

The following questions are designed to measure the impact constipation has had on your daily life **during the past 2 weeks**. For each question, please tick one box.

The following questions ask you about the intensity of your symptoms. To what extent, during the past 2 weeks...	**Not at all**	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
1. have you felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. have you felt heavy because of your constipation?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. How much of the time, during the past 2 weeks...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
3. have you felt any physical discomfort?	☐	☐	☐	☐	☐
4. have you felt the need to open your bowel but not been able to?	☐	☐	☐	☐	☐
5. have you been embarrassed to be with other people?	☐	☐	☐	☐	☐
6. have you been eating less and less because of not being able to have bowel movements?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your <u>daily life</u>. To what extent, during the past 2 weeks...	**Not at all**	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
7. have you had to be careful about what you eat?	☐	☐	☐	☐	☐
8. have you had a decreased appetite?	☐	☐	☐	☐	☐
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	☐	☐	☐	☐	☐
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	☐	☐	☐	☐	☐
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	☐	☐	☐	☐	☐
12. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	☐	☐	☐	☐	☐

The next few questions ask you about your feelings. How much of the time, during the past 2 weeks...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
13. have you felt irritable because of your condition?	☐	☐	☐	☐	☐
14. have you been upset by your condition?	☐	☐	☐	☐	☐
15. have you felt obsessed by your condition?	☐	☐	☐	☐	☐
16. have you felt stressed by your condition?	☐	☐	☐	☐	☐
17. have you been less self-confident because of your condition?	☐	☐	☐	☐	☐
18. have you felt in control of your situation?	☐	☐	☐	☐	☐
The next questions ask you about your feelings. To what extent, during the past 2 weeks...	**Not at all**	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
19. have you been worried about not knowing when you are going to be able to open your bowels?	☐	☐	☐	☐	☐
20. have you been worried about not being able to open your bowels when you needed to?	☐	☐	☐	☐	☐
21. have you been more and more bothered by not being able to open your bowels?	☐	☐	☐	☐	☐

The next questions ask about <u>your life with constipation</u>. How much of the time, during the past 2 weeks...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
22. have you been afraid that your condition will get worse?	☐	☐	☐	☐	☐
23. have you felt that your body was not working properly?	☐	☐	☐	☐	☐
24. have you had fewer bowel movements than you would like?	☐	☐	☐	☐	☐

The next questions ask you about <u>how satisfied</u> you are. To what extent, during the past 2 weeks...	**Not at all**	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
25. have you been satisfied with how often you open your bowels?	☐	☐	☐	☐	☐
26. have you been satisfied with the regularity with which you open your bowels?	☐	☐	☐	☐	☐
27. have you been satisfied with your bowel function?	☐	☐	☐	☐	☐
28. have you been satisfied with your treatment?	☐	☐	☐	☐	☐

APPENDIX 8 – BOWEL DIARY

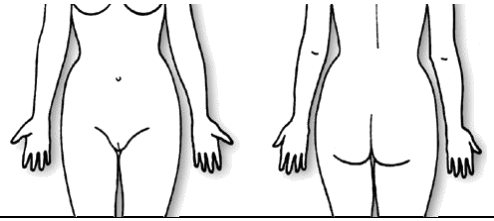
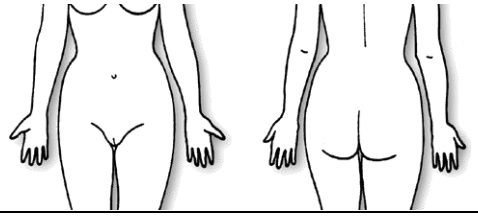
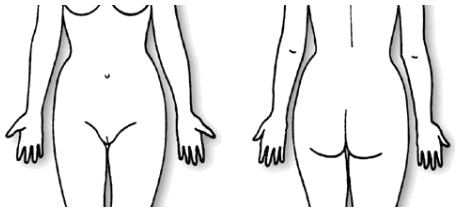
MONASH University
Medicine, Nursing and Health Sciences

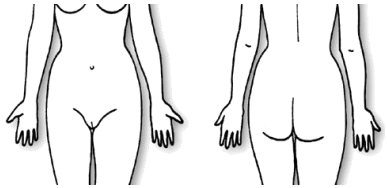
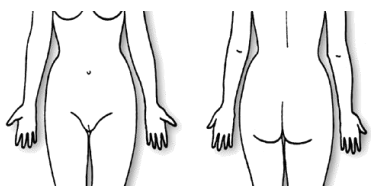
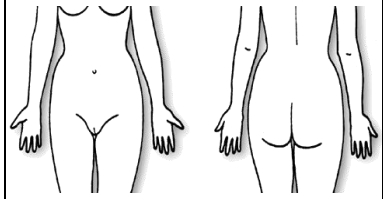
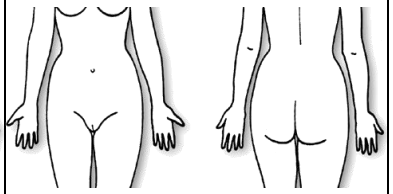
BOWEL DIARY

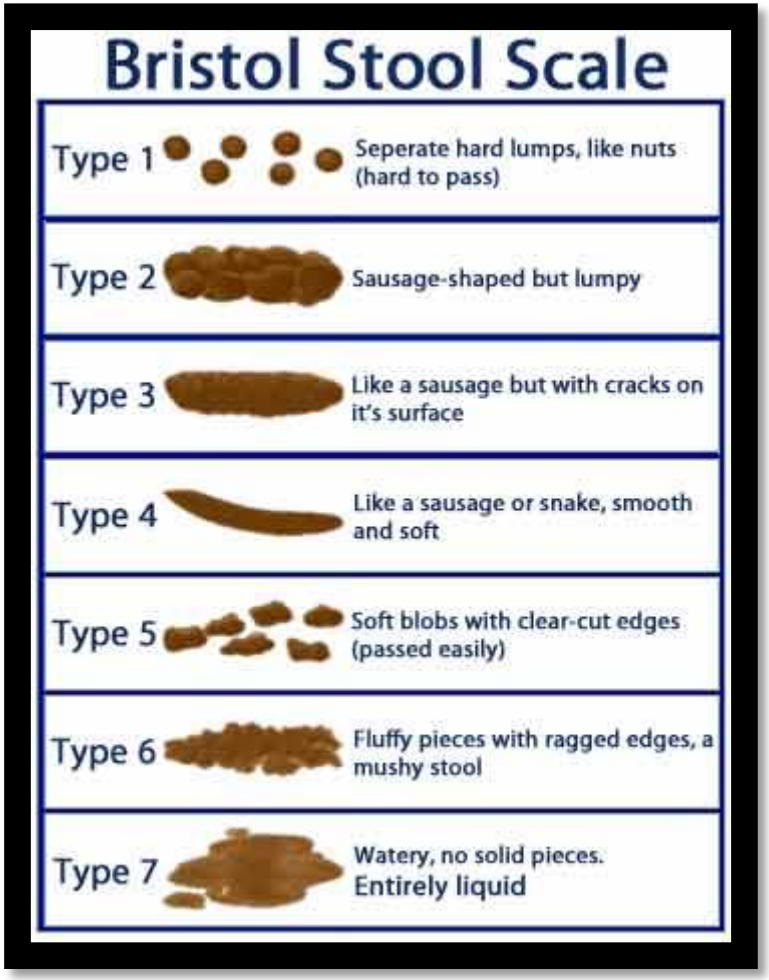
De-TEST Constipation

Study ID _____ **date:** _____

Week:	**Pre study**	□	**Week 3**	□	**End of study**	□
	3 months	□	**1 year**	□		

BOWEL MOTIONS	**Day 1**	**Day 2**	**Day 3**
How many? **How many failed attempts?** **Type** **(see Bristol stool scale at the end)** **How many complete BM?** **Number of times you needed to strain?** **Number of times you needed to use hand/fingers to assist?**	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____
Laxatives **Name?** **What time?** **How many?**	_____ _____ _____	_____ _____ _____	_____ _____ _____
Please shade in on the picture where you felt the urge or pressure to go			

BOWEL MOTIONS	Day 4	Day 5	Day 6	Day 7
How many? **How many failed attempts?** **Type** **(see Bristol stool scale)** **How many complete BM?** **Number of times you needed to strain?** **Number of times you needed to use hand/fingers to assist?**	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____
Laxatives **Name?** **What time?** **How many**	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____
Please shade in on the picture where you felt the urge or pressure to go				


Bristol Stool Scale
Type 1
Seperate hard lumps, like nuts (hard to pass)
Type 2
Sausage-shaped but lumpy
Type 3
Like a sausage but with cracks on it's surface
Type 4
Like a sausage or snake, smooth and soft
Type 5
Soft blobs with clear-cut edges (passed easily)
Type 6
Fluffy pieces with ragged edges, a mushy stool
Type 7
Watery, no solid pieces.
Entirely liquid