Chronic Childhood Constipation: Novel Approaches to Diagnosis and Management

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Dedication

I would like to dedicate this thesis to my parents without whose love and unerring support I wouldn't, and indeed couldn't, be where I am now. Thank you.

Acknowledgement

First and foremost my thanks must go to my mentor and supervisor Professor Hutson. Words cannot describe how much I have learnt over the past few years whilst being under his tutelage. I will always be in debt to him for having enough faith in me to appoint me and then continually support me for the duration of my research.

Two very special people without whom on many occasions I may well have packed up and gone home are Janet Chase and Shirley d'Cruz. They both have been my family away from home and I am so proud to have met them and spent time with them. I look forward to many (happy) shared memories in the future and will miss our daily laughter...and tears!

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Published work contained in this thesis

1. Clarke MC, Chow CS, Chase JW, Gibb S, Hutson JM, Southwell BR. Quality of life in children with slow transit constipation. Journal of Pediatric Surgery 2008; 43: 320-324.
2. Clarke MCC, Southwell BR, Hutson JM. 'Constipation'. In: Paediatric Surgery: Diagnosis and Management. Prof P Puri and Prof M Hollwarth (Eds). In press.
3. Clarke MCC, Chase JW, Gibb S, Robertson V, Catto-Smith A, Hutson JM, Southwell BR. Decreased colonic transit time following transcutaneous interferential electrical stimulation in children with slow transit constipation. Journal of Pediatric Surgery 2009; 44(2): 408-12.
4. Clarke MCC, Chase JW, Gibb S, Catto-Smith A, Hutson JM, Southwell BR. Standard medical therapies do not alter colonic transit time in children with treatment-resistant constipation. Paediatric Surgery International 2009; 25(6): 473-8.
5. Clarke MCC, Chase JW, Gibb S, Hutson JM, Southwell BR. Improvement of quality of life in children with slow transit constipation following treatment with transcutaneous electrical stimulation. Journal of Pediatric Surgery 2009. 44(6): 1268-72.
6. Chase JW, Clarke MCC, Gibb SM, Catto-Smith AG, Robertson VJ, Hutson JM, Southwell BR. Transcutaneous electrical stimulation increases colonic activity in paediatric slow transit constipation; Submitted to Gastroenterology for consideration for publication.

Related publications

1. Sutcliffe J, King SK, Clarke MC, Farmer P, Hutson JM, Southwell BR. Reduced distribution of pacemaking cells in dilated colon. Pediatric Surgery International 2007; 23(12):1179-82.
2. Reilly DJ, Chase JW, Hutson JM, Clarke MCC, Gibb S, Stillman B, Southwell BR. Connective tissue disorder - a new subgroup of boys with slow transit constipation. Journal of Pediatric Surgery 2008; 43(6): 1111-4.
3. Hutson JM, Chase JW, Clarke MCC, King SK, Sutcliffe J, Gibb S, Catto-Smith AG, Robertson VJ, Southwell BR. Slow transit constipation in children: our experience. Accepted for publication in Paediatric Surgery International.
4. Southwell BR, Clarke MCC, Sutcliffe J, Hutson JM. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. Accepted for publication in Paediatric Surgery International.
5. Chase JW, Stillman BC, Gibb S, Clarke MCC, Robertson VJ, Catto-Smith AG, Hutson JM, Southwell BR. Reduced trunk muscular control in children with slow transit constipation. Accepted for publication in Journal of Gastroenterology and Hepatology.

Presentations at international conferences

1. Colonic manometry and transcutaneous stimulation (using interferential therapy) in slow transit constipation. Clarke MCC, King SK, Chase JW, Gibb S, Southwell BR, Hutson JM. International Symposium on Pediatric Surgical Research, Florence, Italy. October 2006. Oral presentation.
2. Colonic motility in children. Clarke MCC (invited speaker). Gastroenterological Society of Australia (GESA), Adelaide, Australia. October 2006. Oral presentation.
3. Quality of life in children with slow transit constipation. Clarke MCC, Chow CS, Chase JW, Gibb S, Hutson JM, Southwell BS. British Association of Paediatric Surgeons (BAPS), Edinburgh, Scotland. July 2007. Oral presentation.
4. Quality of life is low in children with slow transit constipation. Clarke MCC, Chow CS, Chase JW, Gibb S, Hutson JM, Southwell BS Gastroenterological Society of Australia (GESA), Perth, Australia. October 2007. Oral presentation.
5. Decreased colonic transit time following transcutaneous interferential electrical stimulation in children with slow transit constipation. Clarke MCC, Chase JW, Gibb S, Robertson V, Catto-Smith A, Hutson JM, Southwell BS. British Association of Paediatric Surgeons (BAPS), Salamanca, Spain. July 2008. Oral presentation.
6. Improvement of quality of life in children with slow transit constipation following treatment with transcutaneous electrical stimulation. Clarke MCC,

Chase JW, Gibb S, Hutson JM, Southwell BS. American Academy of Pediatrics (AAP) - Surgical Section, Rosenkrantz Research Prize Paper, Boston, USA, October 2008. Oral presentation.

7. Increased colonic activity in children with slow transit constipation, as measured by colonic manometry, after treatment with transcutaneous electrical stimulation. Clarke MCC, King SKK, Stanton M, Chase JW, Gibb S, Robertson V, Catto-Smith A, Hutson JM, Southwell BS. British Association of Paediatric Surgeons (BAPS), Graz, Austria, July 2009. Poster Presentation.

Declaration

I personally performed all of the research in this thesis with the following exceptions:

Chapter 4 - some of the questionnaires were administered (under my supervision) by Chee-Seng Chow (AMS medical student, University of Melbourne). All of the data analysis was performed alone.

Chapters 5 and 8 - The nuclear transit studies were performed by the radiology staff at The Royal Children's Hospital, Melbourne and Monash Medical Centre, Melbourne. Having been provided with the raw data, the geometric centre of activity calculations and the subsequent data analysis were undertaken alone.

Chapters 6, 7, 8 and 9 - I was part of a team who undertook to perform a randomised controlled partial-crossover trial at The Royal Children's Hospital, Melbourne, investigating the possible role of interferential electrical stimulation in the management of children with slow transit constipation. I was not involved in either the original ethics application or the design of the trial, both of which were performed prior to my appointment as a trial coordinator. As a trial coordinator my role, along with Janet Chase (Physiotherapist, Royal Children's Hospital, Melbourne) was that of participant recruitment and management along with subsequent applications for ethics modification. Susie Gibb performed the majority of clinical examinations however, I stepped into this role when she was unavailable. My additional roles included questionnaire formation and administration and I was

responsible for establishing the trial databases and performing data entry (along with Janet Chase). I performed all data analysis alone. Overseeing the running of the trial were Prof Val Robertson (Physiotherapist, University of Newcastle, New South Wales), A/Prof Tony Catto-Smith (Consultant Paediatric Gastroenterologist, Royal Children's Hospital, Melbourne), Dr Bridget Southwell (Head of Surgical Research, Murdoch Children's Research Institute, Melbourne) and Prof John Hutson (Paediatric Consultant, Department of General Surgery, Royal Children's Hospital, Melbourne).

Chapter 9 - Some of the pre-trial manometric studies were performed by my predecessors Dr Sebastian King (PhD Research Student, Royal Children's Hospital, Melbourne) and Dr Jonathan Sutcliffe (MD Research Student, Royal Children's Hospital, Melbourne). All of the studies were carried out with the assistance of Ms Di Simpson, Clinical Nurse Specialist, Department of Gastroenterology, Royal Children's Hospital, Melbourne. Fluoroscopic screening to ascertain the position of the manometry catheter was performed with the help of the radiography staff, Royal Children's Hospital, Melbourne.

Melanie C C Clarke

Ethical considerations

The studies described in chapters 4, 5, 6, 7, 8 and 9 were all granted ethical approval by the Human Research Ethics Committee (HREC) at the Royal Children's Hospital, Melbourne - reference numbers 26174 (Quality of life in children with and without slow transit constipation) and 23040C (Colonic manometry and transcutaneous stimulation (using interferential therapy) in slow transit constipation. Ethical approval was granted for the use of attendants at a Scout Jamboree as control subjects.

In relation to the clinical trial involving the assessment of the application of transcutaneous interferential therapy in children with slow transit constipation, there was no unprecedented contacting of potential recruits by the trial coordinators nor was there any coercion to participate.

Abbreviations used (in the order that they appear in the text):

NASPGHAN - North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

PACCT - Paris Consensus on Childhood Constipation Terminology

STC - Slow transit constipation

FFR - Functional faecal retention

ENS - Enteric nervous system

Ach - Acetylcholine

VIP - Vasoactive intestinal peptide

NO - Nitric oxide

NOS - Nitric oxide synthase

ICC - Interstitial cells of Cajal

CIP - Chronic intestinal pseudo-obstruction

AP - Action potential

SMC - Smooth muscle cell

ITU - Intensive therapy unit

IND - Intestinal neuronal dysplasia

HD - Hirschsprung's Disease

GI - Gastrointestinal

AchE - Acetylcholinesterase

HIV - Human immunodeficiency virus

TPN - Total parenteral nutrition

CCK - Cholecystokinin

Cl^- - Chloride

PGE1 - Prostaglandin E1

CFTR - cystic fibrosis transmembrane conductance regulator

ACE - Antegrade continence enemas

GC - Geometric centre

ROI - Regions of interest

TCTT - Total colonic transit time

SD - Standard deviation

CTT - Colonic transit time

GITT - Gastrointestinal transit time

SE - Standard error

SEM - Standard error of the mean

TGITT - Total gastrointestinal transit time

HAPS - High amplitude propagating sequences

HARPS - High amplitude retrograde propagating sequence

RMC - Rectal motor complex

MI - Motility index

TENS - Transcutaneous Electrical Nerve Stimulation

IFT - Interferential therapy

SNS - Sacral nerve stimulation

FEA - Finite element analysis

PHI - Peptide histidine isoleucine

NPY - Neuropeptide Y

LOS - Lower oesophageal sphincter

EGG - Electrogastrography

IBS - Irritable bowel syndrome

QoL - Quality of life

HR-QoL - Health-related QoL

VAS - Visual analogue scales

FIQL - Fecal Incontinence Quality of Life Scale

PAC-QOL - Patient Assessment of Constipation Quality of Life Questionnaire

ASCRS - American Society of Colon and Rectal Surgeons

GIQLI - Gastrointestinal Quality of Life Index

MMHQ - Modified Manchester Health Questionnaire

FISI - Faecal Incontinence Severity Index

MHQ - Manchester Health Questionnaire

PAC-SYM - Patient Assessment of Constipation Symptoms

CHQ - The Child Health Questionnaire

SF-10 - Short form-10

CHIP - The Child Health and Illness Profile

HAY - The How Are You Questionnaire

WHO - World Health Organisation

PedsQL - Pediatric Quality of Life Questionnaire

HREC - Human Research Ethics Committee

ADHD - Attention deficit hyperactivity disorder

RCT - Randomised Controlled Trial

CCTR - Cochrane Controlled Trials Register

NTS - Nuclear transit study

RCH - Royal Children's Hospital

MMC - Monash Medical Centre

T%R - Total percent retention

MAP - mean activity position

δ - Difference

TFT - Thyroid function tests

FBC - Full blood count

APS - Antegrade propagating sequence

RPS - Retrograde propagating sequence

Abstract

Introduction

This thesis describes the aetiology, pathology, diagnosis and management of children with constipation. In particular, it describes a condition, slow transit constipation, which represents a form of chronic childhood constipation that is not readily responsive to conventional treatment.

Hypothesis and aims

Firstly this thesis hypothesises that quality of life is affected by slow transit constipation when subjects are compared to healthy age matched controls. Secondly, it proposes to ascertain whether or not nuclear scintigraphy represents a reliable means of assessing colonic motility. Thirdly, it seeks to determine whether or not transcutaneous electrical stimulation (in the form of interferential therapy) has the ability to alter either the clinical symptoms, quality of life or colonic transit of children with slow transit constipation. Lastly, this thesis aims to look at a subgroup of children with slow transit constipation managed by antegrade continence enemas delivered via an appendix stoma, and determine whether or not colonic activity, measured by a manometric catheter inserted via their appendicostomy, is affected by transcutaneous inferential therapy.

Methods

Study 1 - Children (8-18yrs) with symptoms of constipation and proven slow transit constipation on nuclear scintigraphy, with symptoms for >2years unresponsive to conventional dietary, medical and behavioural therapies, were recruited from

gastrointestinal and surgical out-patient clinics. Control subjects were recruited from a local scout jamboree. QoL was assessed using the PedsQL tool that consists of parallel parent and child reported scores. Physical, psychosocial and total quality of life scores were compared using Wilcoxon matched pairs and Mann Whitney tests.

Study 2 - Children (8-18yrs) with symptoms of constipation for >2years unresponsive to conventional dietary, medical and behavioural therapies, who had had 2 nuclear transit studies performed on separate occasions were recruited from gastrointestinal and surgical out-patient clinics. Geometric centres of radioactivity were compared at 6, 24, 30 and 48hrs. The GC at each time point for the initial and repeat studies were compared by parametric statistical analysis (paired t-test).

Study 3 - Children (8-18yrs) with symptoms of constipation and proven slow transit constipation on nuclear scintigraphy, with symptoms for >2years unresponsive to conventional dietary, medical and behavioural therapies, were recruited from gastrointestinal and surgical out-patient clinics. Children were randomised to receive either real or placebo interferential therapy consisting of 12 treatment sessions over a 4 week period. Frequency of defecation, soiling and abdominal pain were assessed before, during and after intervention. Quality of life scores (PedsQL, Holschneider and Templeton) and gastrointestinal transit time (nuclear scintigraphy) were also evaluated before and after treatment. Data were analysed using independent sample and paired *t* tests. Where the data were not normally distributed, either Mann Whitney or Wilcoxon matched pairs testing was performed.

Study 4 - Children (8-18yrs) with symptoms of constipation and proven slow transit constipation on nuclear scintigraphy, with symptoms for >2years unresponsive to conventional dietary, medical and behavioural therapies, with pre-existing appendix

stomas were recruited from gastrointestinal and surgical out-patient clinics. Subjects received the same intervention as described in study 3 with all participants receiving real interferential therapy. Colonic activity was assessed pre- and post-intervention by colonic manometry - the catheter having been inserted in an antegrade fashion via the appendicostomy. Data were analysed using paired *t* tests.

Results

Study 1 - Subjects with slow transit constipation (n=51) described significantly poorer quality of life than age matched controls (n=79). This was so for total child reported ($p = < 0.0001$) and parent reported ($p < 0.0001$) scores. Reported scores for subjects with slow transit constipation were comparable to other chronic disease states.

Study 2 - 7 children were recruited in whom 2 nuclear transit studies had been performed. There was no statistical difference between the 2 studies when comparing mean geometric centre of radioactivity at 6hrs ($p = 0.161$), 24hrs ($p = 0.780$), 30hrs ($p = 0.947$) and 48hrs ($p = 0.615$).

Study 3 - 35 children were recruited, 18 of whom were randomised to receive real interferential therapy. There were no statistical differences between the 2 groups. There was no change in frequency of defecation or soiling. There was a small improvement in episodes of abdominal pain in the group that received real treatment ($p = 0.05$). There appeared to be a decrease in colonic transit time as measured by nuclear scintigraphy after intervention with real interferential therapy. There was a significant difference in the post-intervention GC between the 2 treatment arms at 24 ($p = 0.004$), 30 ($p = 0.02$) and 48 ($p = 0.002$) hours. Comparing the 2 treatment

groups before and after intervention there was no change in quality of life scores. When looking at each individual treatment arm, children described a significant improvement in their quality of life (PedsQL scores) after real interferential therapy ($p = 0.005$).

Study 4 - 5 children underwent colonic manometry before and after treatment with inferential therapy. There was a small increase in antegrade colonic activity following intervention $p = 0.03$. No other measured parameters were affected (amplitude, duration, velocity and regional linkage). There was no statistical difference in their frequency of episodes of defecation, soiling or abdominal pain.

Conclusion

This thesis concludes that quality of life is adversely affected by slow transit constipation and that evaluation of quality of life should be part of routine assessment of children with constipation. It also proposes that nuclear scintigraphy represents a reliable means of assessing colonic transit in states of colonic inertia such as slow transit constipation. Lastly, having demonstrated varied subjective and objective responses to its application, it proposes that further evaluation is required to evaluate the potential use of interferential therapy in children with slow transit constipation.

1. Constipation

1. Constipation

1.1 Introduction

Constipation is one of the most common conditions affecting western society. Its prevalence is between 5 and 30%, depending on the diagnostic criteria utilised [1]. Gastrointestinal motility is affected by genetic, organic, environmental and psychological factors. Many different aetiological factors can result in the common features of decreased bowel frequency or impaired rectal evacuation or recurrent faecal soiling. The diagnosis of constipation requires careful history-taking, thorough examination and individually tailored investigation.

1.2 Constipation in children

Constipation occurs in around 3% of children and accounts for 3-5% of visits to paediatricians and 10-25% of referrals to gastroenterologists [2-5]. A positive family history can be found in 28-50% of constipated children and a higher incidence has been reported in monozygotic than dizygotic twins. The peak incidence of constipation occurs at the time of toilet training (between 2 and 4 years of age), with an increased prevalence in boys.

1.3 Definition of constipation

There is much discrepancy concerning the definition of constipation. In part this is due to the wide range of what is perceived as a normal stooling pattern. Definitions can be based on stool frequency, stool consistency, ease of defecation and associated symptoms such as soiling, bloating and abdominal pain. Although it is often accepted that there is no precise definition of constipation that encompasses all

people, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) describes it as a "*delay or difficulty in defecation present for 2 weeks or more*" [6]. More recently, the Paris Consensus on Childhood Constipation Terminology (PACCT) group [7] has defined chronic constipation in children as the occurrence of 2 or more of the following characteristics during the previous 8 weeks:

- Less than 3 stools per week
- More than one episode of faecal incontinence per week
- Large stools in the rectum or palpable on abdominal examination
- Passing of very large stools that obstruct the toilet
- Retentive posturing and withholding behaviour
- Painful defecation

Faecal incontinence is defined as "*the passage of stools in an inappropriate place*" and has been chosen as a term to replace "encopresis" or "soiling". It can be either organic (caused by an identifiable neurochemical, neuroendocrinologic or structural anomaly) or functional in origin with functional faecal incontinence being further classified as (i) constipation-associated: *the passage of stools in inappropriate places by a child with a mental age of 4 years or older where the behaviour is associated with constipation* or (ii) non-retentive: *the passage of stools in inappropriate places by a child with a mental age of 4 years or older who shows no evidence of constipation by history and /or examination*.

A normal bowel habit is defined by NASPGHAN as "*having between 3 movements a week and 3 movements a day with stools that are brown or golden brown and formed, with a texture similar to peanut butter, and a size and shape similar to a sausage*" [6]. The frequency of stooling will also vary with age and, in babies, how they are fed [8] (Table 1):

Table 1 - *Age related frequency of stooling in children.*

• 0-3 months (breast fed)	5-40 motions/week
• 0-3 months (formula fed)	5-20 "
• 6-12 months	5-28 "
• 1-3 years	4-21 "
• >3 years	3-14 "

1.4 Normal defecation

Defecation is the act or process by which solid or semisolid waste material (faeces) is eliminated from the digestive tract via the anus. It is a complex process that requires precise co-ordination of contraction and relaxation of both voluntary and involuntary muscles. The rectum acts as a temporary storage facility for the faecal material. It is about 12 cm long, and although at its commencement its calibre is similar to that of the sigmoid colon, near its termination it is dilated to form the rectal ampulla. Defecation is usually stimulated by rectal distension that is detected by stretch receptors situated in the wall of the rectal ampulla. It has also been suggested that sensory receptors in the pelvic floor relay signals to the brain when stool first arrives in the rectum [9]. The firing of the stretch receptors in the ampulla initially triggers the

'recto-anal inhibitory reflex'. This involves relaxation of the internal anal sphincter in association with contraction of the external anal sphincter and the puborectalis segment of levator ani. As stretching increases, and the 'defecation threshold volume' is reached, an urge to defecate is perceived. The rectum shortens and widens (the anorectal angle increases from 90-110° to 135 °) as puborectalis relaxes and evacuation occurs by rectal wall peristalsis accompanied by an increase in intra-abdominal pressure. The act of defecation is made easier by appropriate posture. Leaning forward whilst seated with the feet supported lengthens the anal opening and widens the anorectal angle.

1.5 Aetiology of childhood constipation

Constipation is either organic or functional in origin, with the majority of children having no organic basis for their symptoms [4]. Organic causes of childhood constipation include congenital anatomic or structural defects, metabolic and endocrine disorders, neurological disorders, connective tissue disorders, gastrointestinal disorders, cystic fibrosis and medications (Table 2). Any child with ongoing constipation should have an organic cause for their constipation excluded before a diagnosis of functional constipation is made.

Table 2 - *Causes of constipation in children.*

Congenital anatomic or structural defects
imperforate anus or anal stenosis
anteriorly displaced anus
meconium plug syndrome
Hirschsprung's disease
pelvic mass
abnormal abdominal musculature - prune belly, gastroschisis, Down's syndrome
Metabolic and endocrine disorders
diabetes insipidus
hypercalcaemia and hypokalaemia
renal tubular acidosis
hypothyroidism
dehydration
multiple endocrine neoplasia type 2B
Chronic intestinal pseudo-obstruction
Cystic fibrosis
Connective tissue disorders - scleroderma, systemic lupus erythematosus, Ehlers-Danlos syndrome
Coeliac disease
Neurologic causes
damage to the spinal cord - meningomyelocele, trauma, surgery, tumours, cauda equina syndrome and tethered cord
cerebral palsy
infectious polyneuritis
amyotonia congenita
muscular dystrophy
degenerative disorders
neurofibromatosis
Cow milk intolerance or other food allergies
Other causes
colonic dysmotility (Slow Transit Constipation - STC)
outlet obstruction (Functional Faecal Retention - FFR)
Dietary
poor fibre intake
poor fluid intake
Medication
analgesics (Codeine preparations)
antacids
anticholinergics
anticonvulsants
tricyclic anti-depressants
β-blockers
iron and calcium supplements
antispasmodics
diuretics

Behavioural causes
learned pattern of defecation (can be due to previous painful defecation)
adverse life event
defiant behaviour
intellectual disability

Functional constipation is diagnosed in those children where there is no objective evidence of an underlying pathological condition and is defined by the Rome III criteria (Table 3) [10 11]. The majority of children with functional constipation have a dietary cause for their constipation, functional faecal retention (FFR) or both. Children with FFR exhibit a stool-withholding pattern of defecation. It is believed that this pattern develops due to previous painful defecating experiences that lead to voluntary withholding of faeces in order to avoid further painful defecation [4 6]. It is estimated that up to 63% of children with constipation and soiling have had a history of painful defecation which began when they were under 3 years of age [12]. Alternatively, the initial insult can be as a result of toilet training, changes in routine or diet, stressful events, intercurrent illness, perianal irritation (nappy rash or group A, β-haemolytic streptococcus infection), unavailability/dislike of toilets or postponement of defecation due to lack of interest or attention [6]. This manner of stooling results in prolonged faecal colonic stasis, with increased reabsorption of faecal fluid, and leads to an increase in the size and consistency of the stools. Overflow diarrhoea or soiling is the result of watery faecal matter trickling around retained, hardened faeces. With time the rectum becomes accustomed to the constant stimulus of a faecal mass and the normal urge to defecate is lost. This decrease in rectal sensation also means that the child is often unaware of the unintentional passage of faecal matter.

Table 3 - *Rome III criteria for diagnosis of functional constipation* [10].

Diagnostic Criteria for Functional Constipation (Rome III)
Must include two *or more* of the following in a child with a developmental age of *at least* four years
Two or fewer defecations in the toilet per week
At least one episode of faecal incontinence per week
History of retentive posturing or excessive volitional stool retention
History of painful or hard bowel movements
History of a large faecal mass in the rectum
History of large diameter stools that may obscure the toilet
Criteria must be fulfilled at least once per week for at least two months before diagnosis

1.6 Idiopathic constipation

Children with no obvious organic cause for their constipation should be managed by a combination of dietary changes, laxatives and/or stool softeners and/or bulking agents and behavioural modification and toilet training. Toilet posture education and pelvic floor muscle training by a physiotherapist should be considered. Seventy percent of children presenting with constipation will respond to this treatment strategy within 2 years [13 14].

1.7 Treatment-resistant constipation

Thirty percent of children with constipation fail to respond to medical management. They are said to have treatment-resistant or "chronic" constipation. Until recently it was believed that most children with treatment-resistant constipation had a functional or behavioural basis for their symptoms [15]. This is now not the case, with a definite

population of children with chronic constipation having been shown to have a novel condition called slow transit constipation (STC).

1.8 Slow transit constipation (STC)

Idiopathic slow transit constipation (STC) describes a clinical syndrome characterised by intractable constipation that is not readily responsive to laxatives, diet or a change in lifestyle [16]. It is characterised by delayed colonic transit without an underlying systemic disorder or pelvic floor dysfunction. Although it was initially described in young women of reproductive age [17 18] it has now been recognised as a condition affecting children of all ages [19]. Up to 50-60% of children with chronic treatment-resistant constipation may have slow colonic transit [20]. Recently, it has been suggested that STC may be part of a pan-enteric disorder as alterations in oesophageal motility [21], gastric emptying [21 22] and small bowel motility [23 24 25] have been observed in some patients with STC.

1.9 The pathology of slow transit constipation

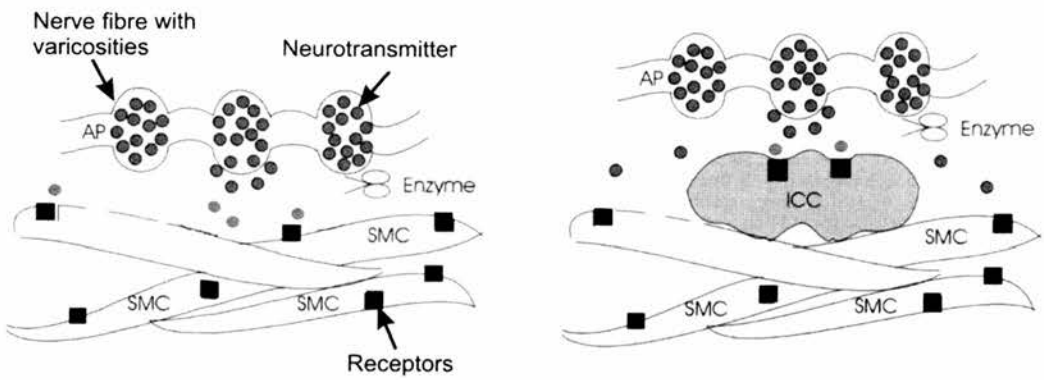
It is believed that in children with STC, the primary defect lies within the enteric nervous system (ENS) [20]. Both clinical and manometric data suggest that the abnormal motility associated with STC should be considered as neuropathic in nature [26]. The gastrointestinal tract contains its own nerve cell bodies which form an intrinsic network that is connected to the central nervous system via the vagal, coeliac and pelvic nerves. Enteric neurons have cell bodies within ganglia that lie in the myenteric or submucosal plexuses. The cell bodies have processes that penetrate the muscle layers where they release their neurotransmitters. Acetylcholine (ACh)

and tachykinins (including substance P) cause gastrointestinal muscular contraction whilst relaxation is initiated by the release of vasoactive intestinal peptide (VIP), nitric oxide (NO) and ATP.

Some studies have suggested that some patients with STC have an element of subclinical autonomic neuropathy [27-30], in particular, selective small fibre neuropathies [28]. The same authors hypothesise that STC occurring in women post childbirth, or following pelvic surgery, may be as a result of pelvic nerve injury and that in a subgroup of people, STC should be considered a disorder of pelvic autonomic nerves [29].

Most studies using conventional histological methods to examine the colon in subjects with STC have failed to identify consistent abnormalities of the ENS [31-33]. Outdated methods employing silver staining techniques report a reduction in the total number of argyrophilic neurones along with some morphological and axonal abnormalities [34]. It was with the advent of immunohistochemistry that abnormalities in the enteric neurotransmitters and neuropeptides (substance P, vasoactive intestinal peptide (VIP) nitric oxide synthase (NOS), neuropeptide Y and 5-HT) were first reported, however findings have been inconsistent with decreased, increased and unchanged levels all being described [20 35-40]. Although these findings could suggest that alterations of enteric neurotransmitters do not play a major role in the pathophysiology of STC, it is more likely that STC represents a heterogeneous group of disorders with the same end result - delayed colonic transit.

Although they were discovered in 1893 [41], it is only relatively recently that the true importance of interstitial cells of Cajal (ICC) is finally being recognised. ICC are found in the tunica muscularis throughout the gastrointestinal tract and lie between enteric nerve terminals and smooth muscle [42-45] (Figure 1). Although their precise role has remained undetermined for several decades, it is now thought that they act as a conduit for active transmission of electrical slow waves as well as serving as gastrointestinal pacemaker cells. A loss of ICC has been demonstrated in a range of gastrointestinal motility disorders including STC and chronic intestinal pseudo-obstruction (CIP) [46-54].



(a) (b)

Figure 1 - *Old and new models of neuromuscular transmission in the gastrointestinal tract.* (a) Old two cell model. Action potentials travelling along nerve fibres caused release of neurotransmitter from varicosities. Transmitter diffused across extracellular space and bound to receptors on muscle cells inducing contraction or relaxation. (b) New three cell model. Interstitial cells of Cajal have receptors for transmitters and are connected to each other and to smooth muscle cells by gap junctions. ICC form a network

among the smooth muscle cells. Transmitter released from nerve fibres binds to receptors on ICC, modifying excitation with changes conveyed to adjacent ICC and muscle cells by electrical conduction. ICC also act as pacemaker cells generating and conducting rhythmic electrical activity that produces slow waves. AP - action potential; ICC - interstitial cells of Cajal; SMC - smooth muscle cell; ● - transmitter; ■ - receptor [20].

1.10 Diagnosis

1.10.1 Clinical

Medical history and physical examination are essential when diagnosing constipation and a thorough ante-natal/birth/post-natal history should be obtained (Table 4). It is important to clarify what each individual family defines as "constipation" by determining the occurrence of specific symptoms and their frequency. Essential information includes an accurate gastrointestinal and general medical assessment as well as a developmental and psychosocial evaluation. Delayed first passage of meconium, frequent soiling, passage of large soft stools, abdominal distension and bloating are all common features associated with STC.

Table 4 - *Model of history taking and examination in a child with constipation.*

Demographics
Age
Sex

Presenting symptoms
Frequency of defecation
Behaviour associated with defecation
Consistency of stools
Soiling
Pain (abdominal, rectal or other)
Rectal bleeding
Appetite
Vomiting
Abdominal distension
Weight loss/gain
Toilet training
Onset and duration of symptoms

Previous diagnoses and treatments

Current treatment

Peri-natal history
Any ante-natal concerns/diagnoses
Gestation
Birth condition (need for ITU/special care)
Time of passage of meconium

Developmental history
Growth and attainment of developmental markers

Past medical history
Hospital admissions (medical and surgical)
Urinary symptoms
Hypothyroidism associated symptoms

Dietary history

Medications
Immunisations
Allergies

General appearance
Failure to thrive

Routine observations
Height and weight
Pulse
Blood pressure

General examination
Including cardiovascular and respiratory examination

Abdominal examination
Distension
Hepatosplenomegaly
Abdominal mass - including faecaloma
Palpable bowel loops

Neurological and spinal examination
Lower limb - tone, reflexes and power
Sacral dimple/sacral hair tuft
Obvious spinal deformity
Muscle (especially buttock) wasting

Anal inspection
Site
Visible stool (skin and clothing)
Skin condition
Perianal skin tags
Anal fissure

Rectal examination
Anal wink
Anal tone
Pain
Presence/consistency of stool
Pelvic mass
Explosive stool on finger withdrawal
Bleeding

Family history
Gastrointestinal and other significant illnesses
(including thyroid disease, cystic fibrosis,
coeliac disease, neurological conditions,
connective tissue disorders, diabetes)

Psychosocial history
Age appropriate quality of life assessment

A thorough physical examination is essential in the initial assessment of a child with constipation (Table 4). This should include a general examination as well as an abdominal examination and external examination of the perineum and perianal area. A rectal examination should be performed by an appropriately experienced practitioner [20].

Blood samples should be obtained for coeliac disease screening and thyroid function testing. A high percentage of eosinophils in the white cell differential of a full blood count can be seen in cases of cows' milk protein intolerance [20].

1.10.2 Radiological

1.10.2.1 Abdominal X-ray

Plain abdominal x-rays have debatable value in the assessment of constipation [55]. If faecal impaction or loading is obvious on rectal or abdominal examination then little more information can be attained by means of a plain x-ray. On rare occasions an x-ray is useful to identify a vertebral anomaly (e.g. sacral agenesis and Currarino Syndrome). Abdominal x-rays can be used to assess the presence and degree of abdominal loading, especially in obese subjects or in those in whom a rectal

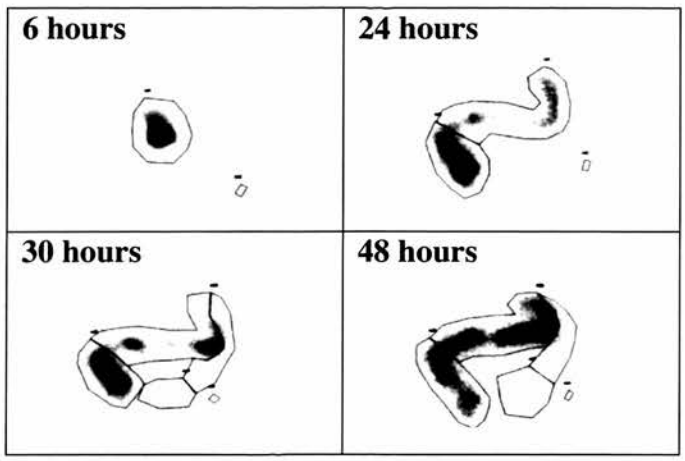
examination is refused or inappropriate, however interpretation can be subjective and x-ray timing in relation to defecation can be misleading.

1.10.2.2 Transit Studies (Overview)

Colonic transit time takes between 1-3 days during which time there is extensive mixing of stool. The quantification of transit time demonstrates the presence of constipation and provides an objective evaluation of faecal clearance. Transit time has traditionally been measured using plastic, non-absorbable radio-opaque markers with transit time in different regions being determined by the ingestion of different shaped markers over 3-6 days [56-59]. Studies measuring normal transit in children give the upper range of total colonic transit from 46-62 hr [60]. Transit rates in children less than 5 years old are faster, whilst children aged 6 years or more have a range of transit and frequency of defecation similar to adults. This mode of assessment of gastrointestinal transit time is widely available and until recently has been considered the gold standard. However, it has now been recognised that indigestible solid particles do not move with a meal, and may not be handled by the colon in the same manner as stool [61]. Consequently, gastrointestinal transit is increasingly being investigated using scintigraphy (nuclear transit study) [62-70]. A tracer dose of technetium, or gallium, in 20ml of milk is ingested and images obtained at 0-2 hours to assess gastric emptying and a further image at 6 hours to ascertain whether or not the tracer has reached the colon. Subsequently, images are obtained at 24, 30 and 48 hours to document transit through the colon. The colonic transit index can be obtained based on the geometric mean of intestinal activity at 6, 24, 30 and 48 hours (and 72 hours for adults) post-ingestion of tracer. By this means, patients with small

bowel, right, left or pan-colonic (STC) or pan-intestinal transit deficits can be distinguished form those with normal gastrointestinal transit with FFR (Figure 2).

(a)



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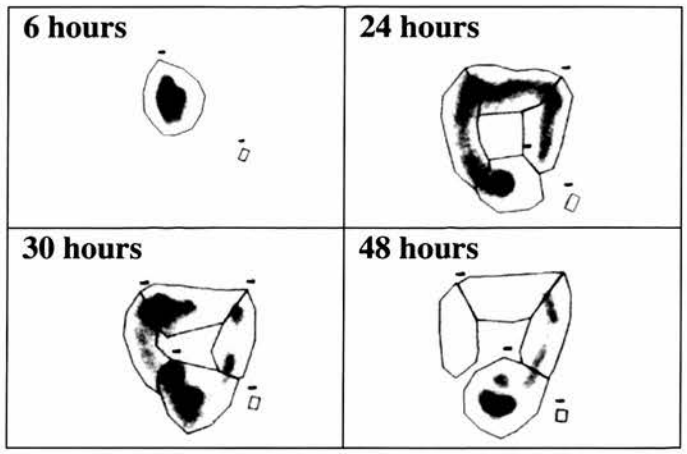


Figure 2 - *Nuclear transit studies demonstrating (a) slow transit constipation (STC) and (b) functional faecal retention (FFR)* [20].

1.10.3 Rectal Mucosal Biopsy

In cases of intractable constipation with a history of delayed passage of meconium or symptoms since birth, a diagnosis of Hirschsprung's disease needs to be eliminated

by performing a rectal mucosal biopsy. Biopsy specimens are obtained from approx 3cm above the anal verge and should be deep enough to include adequate submucosa [71]. A diagnosis of Hirschsprung's disease is supported by an absence of ganglion cells, usually in the presence of hypertrophied extrinsic nerve fibres, with a marked increase in acetylcholinesterase activity in the lamina propria and muscularis mucosa [72]. A rectal biopsy is also useful in identifying those children with a food allergy, as recognised by increased eosinophils in the mucosa [20].

1.10.4 Laparoscopic Colonic Biopsies

Recently, in those children with proximal colonic delay demonstrated by their transit study, laparoscopic seromuscular biopsies are being performed in association with rectal biopsy, in some centres, in an attempt to identify any consistent histological anomalies. Biopsies are collected from the hepatic flexure, midtransverse colon, splenic flexure and sigmoid colon without the need for suturing the defect [73]. Specimens are processed for immunofluorescence histochemistry and are stained for substance P, VIP, NOS or cKit (a marker ICC). It has been proposed that some children with STC have a form of intestinal neuronal dysplasia (IND), which represents an abnormality of intestinal innervation that is more subtle than Hirschsprung's disease and can be diagnosed by abnormal immunohistochemistry [73-75].

1.10.5 Colonic Manometry

Colonic manometry involves the in vivo measurement of changes in intraluminal pressure within the colon. A multi-channel water-perfusion or solid-state pressure

recording catheter is sited in the colon in either a retrograde manner via colonoscopy, or an antegrade manner [76], via a pre-existing appendix stoma (Figure 3) or via a naso-colic route.

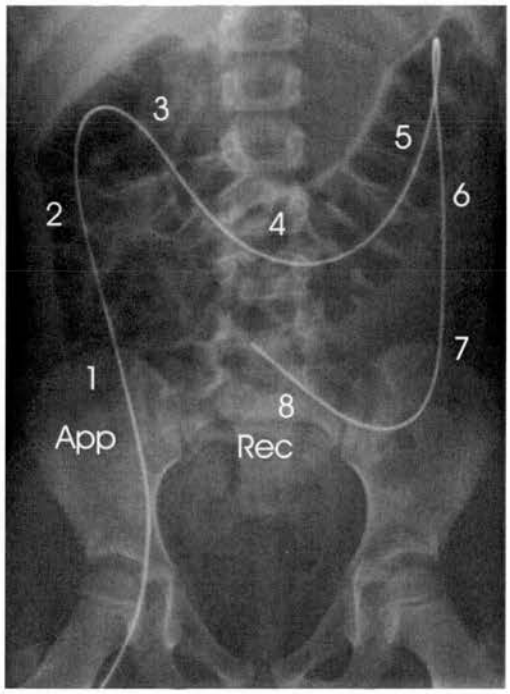
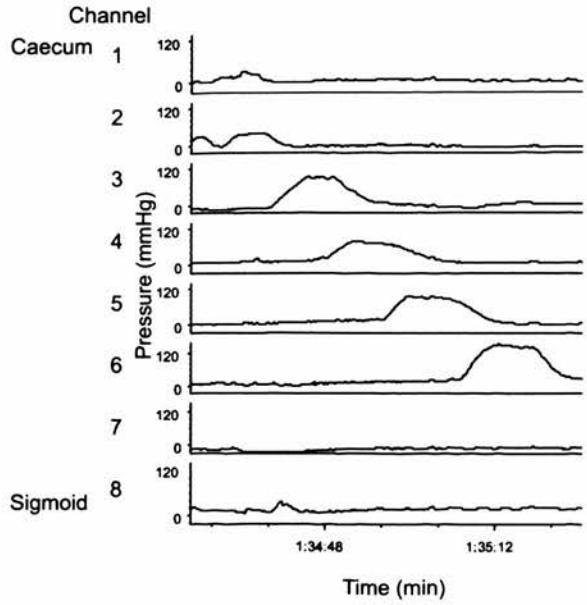


Figure 3 - *Abdominal radiograph showing an antegradely inserted 8 channel manometry catheter passing percutaneously through the appendix (App) to the rectum (Rec) with the position of the side holes shown [76].*

Colonic contractile activity produces changes in intraluminal pressure seen as a deviation from the baseline. Contractions can be non-propagating or propagating with propagating contractions being in either an antegrade or retrograde direction (Figure 4). High amplitude contractions (>116mmHg) are thought to represent mass movement within the colon. Standards for colonic manometry in children have been

defined and parameters measured [77]. Expected frequency of propagating sequences, ratio of antegrade to retrograde contractions, frequency of high amplitude propagating sequences, post-prandial response and diurnal variation have all been determined [77].

(a)



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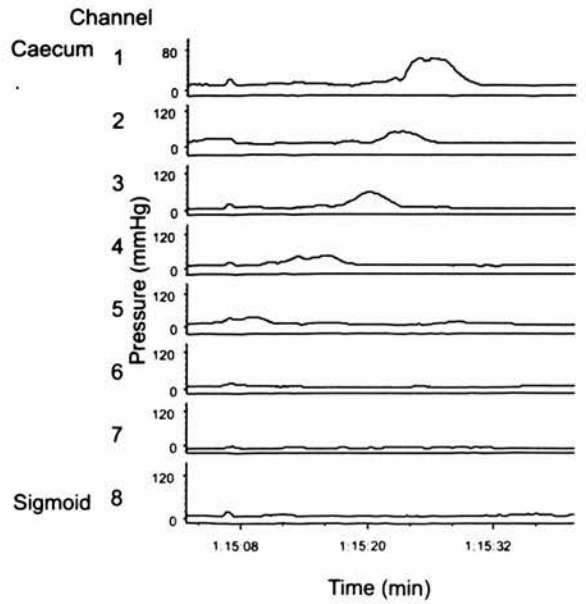

Figure 4 - *Colonic manometry showing (a) an antegrade propagating sequence and (b) a retrograde propagating sequence* [76].

1.11 Differential diagnosis

1.11.1 Hirschsprung's Disease (HD)

This represents a congenital condition where there is abnormal innervation (aganglionosis - absent parasympathetic ganglion cells) of the bowel that results in difficulty stooling. It has an approximate incidence of 1:5,000 live births [71]. HD is associated with a chromosomal abnormality in 12% of cases with an additional 18% of cases having other congenital anomalies [78]. HD is characterized by the absence of intrinsic ganglion cells in the submucosal and myenteric plexuses of the enteric nervous system that is thought to result from premature migration arrest of neural crest cells in the hindgut between 5 and 12 weeks of gestation [79]. There is a wide variation in the possible length of affected bowel, with the disease mostly affecting the distal-most part of the rectum then spreading proximally. The aganglionic bowel is in a constant state of spasm, causing a functional obstruction. HD that has a short aganglionic segment, involving the anal canal, +/- rectum, +/- sigmoid colon, is 5 times more common in males than in females. However, the less common, long segment HD is equally common in males and females and is more likely to have a positive family history [71].

Cases of HD most commonly present in the neonatal period with delay in the passage of meconium (>48 hours after birth), bilious vomiting and non-tender abdominal

distension. Rectal examination with a probe classically causes explosive decompression of meconium through the tight anal sphincters [71].

Plain abdominal radiographs show marked gaseous distension of the bowel proximal to the affected segment (Figure 5). A diagnosis of HD can sometimes be made with a lower gastrointestinal (GI) contrast study. There may be constriction of the segment of bowel affected by the HD tapering through a transition zone to a distended megacolon. However, contrast studies in association with ultrashort- or long-segment disease may appear normal. HD is definitively diagnosed by suction rectal biopsy where a lack of ganglion cells in the affected bowel, along with increased acetylcholinesterase (AChE) staining, is indicative of the condition [71].

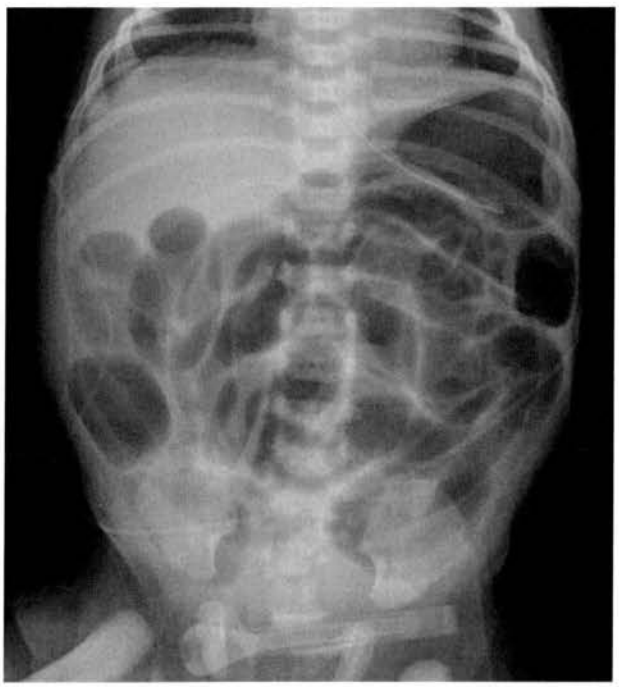

Figure 5 - *Abdominal radiograph in neonate with Hirschsprung's Disease* [71].

Initial management consists of decompression of the bowel either by regular trans-anal washouts or the formation of a defunctioning sigmoid colostomy. Definitive treatment involves performing a "pull-through" operation where the normally innervated bowel is brought down and sutured to the anus at the level of the anal valves [71].

1.11.2 Chronic intestinal pseudo-obstruction (CIP)

Chronic intestinal pseudo-obstruction (CIP) is an intestinal motility disorder that manifests as episodes of intestinal obstruction without mucosal or structural evidence of mechanical blockage and is thought to be as a result of injury to the neural control mechanisms responsible for intestinal peristalsis [80]. There are a variety of known causes of CIP (Table 5) although it most commonly occurs secondary to conditions that impair neuromuscular function. In addition to affecting either the small or the large intestine, CIP can also involve the oesophagus, stomach, ureters and bladder.

The clinical features of CIP are dependent on the organs affected, the duration and severity of illness, any co-morbidities and the degree of resultant nutritional compromise [80]. Early on in the disease, intermittent symptoms of bloating, nausea, pain and erratic defecation are often attributed to recurrent gastrointestinal upset. Symptoms then commonly become more chronic with additional severe, acute exacerbations occurring at irregular intervals, and frequently without identifiable triggers, that often require hospitalisation for intravenous fluid therapy, analgesia and nutritional support [80].

Table 5 - *Causes of chronic intestinal pseudo-obstruction (CIP)* [80].

Primary chronic intestinal pseudo-obstruction
Visceral myopathy (familial or sporadic)
Visceral neuropathy (familial or sporadic)
Normal histology variant (sporadic only)
Secondary chronic intestinal pseudo-obstruction
Drugs
Narcotics
Antidepressants
Anticholinergics
Parkinson's medications
Clonidine
Vincristine
Phenothiazines
Endocrine disorders
Diabetes mellitus
Hypo- or hyperthyroidism
Hypoparathyroidism
Infections
Chagas disease
Cytomegalovirus
Epstein-Barr virus
HIV
Muscle disorders
Scleroderma
Systemic lupus erythematosus
Dermatomyositis
Amyloidosis
Myotonic dystrophy
Progressive or Duchenne muscular dystrophy
Neurologic disorders
Diabetic neuropathy
Parkinson's disease
Dysautonomia
Malignancy affecting neural structures
Multiple sclerosis
Amyloidosis
Paraneoplastic syndromes

Patients should be assessed as for any other cause of constipation/change in bowel habit, with a full history, examination and appropriately tailored investigations. In the first instance, plain abdominal radiographs and contrast studies are important to exclude obstruction. It may then be appropriate to perform oesophageal/duodenal/

small bowel/colonic or anorectal manometry and/or a gastrointestinal transit study to identify any patterns of abnormal motility.

CIP is usually managed by a combination of medical therapy (pharmacological agents that increase intestinal motility) and nutritional support but occasionally requires surgical intervention (endoscopic placement of venting tubes and/or feeding tubes or stomas for intestinal decompression) [81]. Providing adequate oral intake is the biggest problem associated with CIP. Low lactose, low fat and low residue diets have all been proposed as a means of reducing intestinal symptoms. In some patients, symptoms can be so severe that that they require total parenteral nutrition (TPN) in order to maintain an adequate caloric and fluid intake. Complications related to TPN are the commonest cause of death in children with CIP [81].

1.11.3 Intestinal neuronal dysplasia

First described by Meier-Rouge in 1971, intestinal neuronal dysplasia (IND) was initially depicted as a colonic, pseudo-Hirschsprung disorder characterised by hyperganglionosis [82]. It has now been recognised as a condition that can affect any part of the GI tract and has been classified into 2 clinical and histochemical subtypes, A and B [83]. Type A is a rare condition characterised by congenital hypoplasia or aplasia of the sympathetic adrenergic innervation of the intestine. Patients present as infants with diarrhoea, bloody stools and colonic spasticity. In contrast, in the more common type B disease it is the enteric plexus that is primarily affected and presents as intestinal dysmotility, chronic constipation and/or pseudo-obstruction in the first 3 years of life [83].

The aetiology of IND type B remains largely unclear, however it is proposed that it is caused by a reaction of the ENS to intestinal obstruction or inflammatory disease either in the foetal or post-natal period [84]. There is a high incidence of associated anomalies in patients with IND, with one series describing a rate of 30.5%, increasing to 80% when only cases of diffuse disease (cf. rectocolonic) were considered [85]. Associated anomalies include intestinal malrotation, megacystis, congenital short small bowel, hypertrophic pyloric stenosis, necrotising enterocolitis, mental retardation, short stature, facial dysmorphia, Down's syndrome, intestinal atresia, diffuse intestinal angiomatosis, histiocytosis, microvillus agenesis and hearing loss [85].

Diagnosis is often made by histochemical analysis of tissue obtained by rectal suction biopsy. Schärli and Meier-Ruge initially described diagnostic criteria based on the following histochemical findings: (i) increased AchE activity in the lamina propria, (ii) hyperplasia ("giant ganglia") within the submucosal plexus, (iii) heterotopia of neurone cells in the lamina propria mucosa, and (iv) increased AchE activity in the circular muscle layer [86]. These were modified by Borchard et al who state that obligatory histochemical findings are (i) hyperplasia of the submucosal plexus and (ii) increased AchE activity around submucosal vessels [86].

Despite these specific diagnostic criteria, there is much debate surrounding IND, with many clinicians remaining unconvinced about its existence [87-90]. A prospective study looked at the interobserver reliability of three pathologists with respect to the

aforementioned histochemical features, and thus final diagnosis, of IND in rectal biopsy specimens from symptomatic children aged 4 days to 15 years [91]. The authors found that although there was no discrepancy amongst the pathologists in cases where there was aganglionosis (HD, $\kappa = 1$), there was, however, high interobserver variability in those cases without aganglionosis where a diagnosis of either normal or IND was made (κ values close to those expected by chance). The authors concluded that some of the previously documented histological 'abnormalities' may in fact be features of normal immature bowel and recommended that rectal biopsies in children should only be used to confirm, or refute, a diagnosis of HD.

This conclusion is supported by Lumb et al [88] who believe that up to 95% of constipation in children is due to FFR and that IND simply provides concerned parents with a hollow diagnosis. They also believe that finding giant ganglia within the submucosal plexus may be a normal variant rather than a pathological finding [89] and report finding giant ganglia in 76-78 % of normal colonic specimens resected for colonic carcinoma. They conclude that following observations that homeobox Enx (Hox11L1) knockout mice appear to have similar colonic features to those seen in IND type B [92], identifying a human homologue for this mouse gene may circumvent any current histological diagnostic difficulties.

1.11.4 Hypoganglionosis

Hypoganglionosis refers to a condition whereby functional intestinal obstruction occurs in association with histochemical findings of fewer intestinal ganglion cells within the myenteric plexus [93]. However, as with IND, there remains extensive

scepticism concerning its existence as a true clinical entity [94]. As yet, the exact histological criteria for diagnosing hypoganglionosis have not been established and very few articles have been published using morphometric examinations. Taguchi et al [95] have recently suggested that two forms of hypoganglionosis exist; congenital and acquired. They reported a series of twenty four cases of functional intestinal obstruction (excluding HD) requiring either small and/or large bowel resection. Thirteen cases had immature ganglion cells, characterised by either normal or increased numbers of ganglion cells with small nuclei. Seven cases had congenital hypoganglionosis where both the number and size of the ganglion were reduced in association with a decrease in the size of Auerbach's plexus. Four cases had acquired hypoganglionosis with decreased numbers of ganglion cells in association with preservation of the size of Auerbach's plexus. The cases of congenital hypoganglionosis had ongoing problems post resection requiring a combination of partial enteral and continuous parenteral nutrition for survival, whereas the cases of acquired hypoganglionosis all improved. These findings suggest that two separate clinical hypoganglionotic conditions exist, with clinical outcome intimately related to histochemical features.

1.12 Medical management of constipation

Seventy percent of children with constipation will respond to "conventional management" within two years [13 14]. Conventional management consists of dietary modification, laxatives and/or stool softeners and/or bulking agents and behavioural modification and toilet training. Before any medical therapy is initiated it is essential to adequately educate the family, and child, with regards to the pathogenesis of

constipation. It is important for everyone to understand that soiling as a result of overflow incontinence is neither a wilful and defiant action nor a result of bad parenting. It may be necessary to repeat educative measures several times during a management program before they are adequately accepted and understood [6].

1.12.1 Dietary modification

The most common dietary cause of constipation is a low fibre diet. The American Dietetic Society recommends daily intake of 20-35g of fibre, however the current average American daily intake is just 5-14g [96]. Within the GI tract, soluble fibre dissolves easily in water and takes on a soft, gel like texture whilst insoluble fibre passes through in an almost unchanged state. By behaving in this way, fibre acts as a natural stool softener and bulking agent. There are good data to suggest that increasing dietary fibre intake is beneficial in the treatment of childhood constipation [6 97 98-100].

Although an increased fluid intake will not in itself relieve constipation, it is commonly believed that an increased intake of water can provide some symptomatic benefit. An increased water intake is thought to increase faecal water content and produce stools that are softer and easier to pass. Although increasing fluid intake is widely practiced, data are anecdotal and controlled trials have been unable to demonstrate any measurable difference in stool consistency [101 102].

1.12.2 Disimpaction

Before regular maintenance therapy can be commenced it is essential to relieve any distal obstructing faeces by means of disimpaction. Faecal impaction is defined as "a hard mass in the lower abdomen identified during physical examination" or "a dilated rectum filled with a large amount of stool found during rectal examination" or "excessive stool in the colon identified by abdominal radiography" [103]. Disimpaction can either be performed medically, using high dose oral laxatives or rectal therapies, or manually [6]. There have been no randomised trials comparing the efficacy of different methods so the choice of treatment should be tailored to the individual following discussion with the patient and family. Once the impaction has been removed then the treatment concentrates on prevention of recurrence [6].

1.12.3 Laxatives

1.12.3.1 Bulk forming laxatives (psyllium, methylcellulose, polycarbophil)

Taken with water, these laxatives provide additional fibre intake and increase water content and bulk volume of the stool in order to decrease colonic transit time and improve stool consistency [104]. Side effects include bloating and abdominal pain.

1.12.3.2 Emollient laxatives (mineral oil)

Mineral oil decreases faecal water absorption producing softer stools. Anal seepage may occur following initial use and lipoid pneumonia has been described following aspiration [6 104].

1.12.3.3 Hyperosmolar laxatives (lactulose, polyethylene glycol, sorbitol (70%), glycerine, magnesium hydroxide, magnesium citrate)

Sorbitol and lactulose are sugars that are poorly absorbed but hydrolysed by coliform bacteria to lactic, acetic and formic acids. These acid metabolites promote accumulation of fluid within the colon that results in the formation of soft stools. Side effects include bloating, abdominal pain, hypernatraemia and increased flatulence. Magnesium hydroxide and magnesium citrate stimulate the release of cholecystokinin (CCK) which then stimulates gastrointestinal water secretion and motility. Their use should be cautioned in infants as they are susceptible to magnesium overload [6] [104]. Polyethylene glycol (PEG3350, Movicol®, Movicol Paediatric Plain®) is a flexible, water-soluble polymer that is used to create high osmotic pressures. It appears to be superior to other osmotic agents as it is not hydrolysed by coliform bacteria resulting in decreased abdominal bloating and flatulence. As it does not contain any electrolytes, salt and water absorption are not a concern, particularly in patients with cardiac or renal disease [6] [104]. Currently, Movicol Paediatric Plain® is the recommended oral agent for the management of faecal impaction in children (Table 6).

Table 6 - *Suggested Movicol Paediatric Plain® regime for oral management of faecal impaction* [105].

	Number of Movicol Paediatric Plain® sachets						
Age (years)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
2-5	2	4	4	6	6	8	8
6-11	4	6	8	10	12	12	12

1.12.3.4 Stimulant laxatives (senna, aloe, castor oil, bisacodyl, glycerine suppositories)

Stimulant laxatives act by altering fluid and electrolyte transport, gastrointestinal motility or both. Senna and aloe contain anthraquinone, a naturally occurring polycyclic aromatic hydrocarbon that alters the absorption and secretion of water in the terminal ileum and colon and causes potassium retention. Its mechanism of action is unknown. Anthraquinones are widely used in the industrial industry as dyes and a side effect of their use in humans can be discoloration of the colonic mucosa (melanosis coli (Figure 6)). This appearance is harmless and reversible upon cessation of use [106]. Bisacodyl stimulates gastrointestinal peristalsis and also alters transmucosal active fluid and electrolyte transport. As with the anthraquinones its mechanism of action remains unknown [107]. Bisacodyl is not tolerated in many subjects due to severe abdominal cramps and the dose should be titrated with tolerance [6 104]. Glycerine is a hyperosmotic stimulant laxative that increases stool water content and also provokes local muscle contraction.

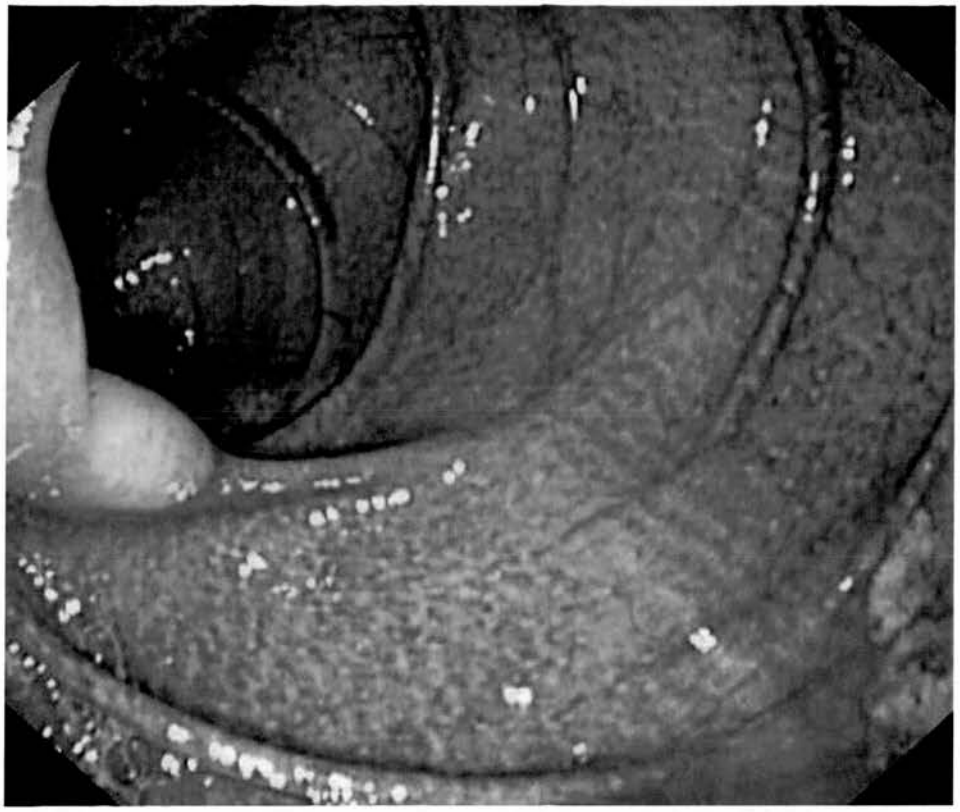

Figure 6 - *Endoscopic picture of colonic wall exhibiting melanosis col[106]i.*

1.12.3.5 Increased chloride (Cl^-) secreting agents (prostaglandin E1 (PGE1), Cl^- channel activators (Lubiprostone®)

Chloride channels are pore-forming proteins that allow the transport of chloride ions across cell membranes. Chloride channels help to maintain the resting membrane potential of skeletal muscle, assist with the depolarisation of smooth muscle, regulate postsynaptic transmission, maintain intracellular pH and moderate cell volume and fluid transport [108]. Several of these actions are critical in maintaining normal gastrointestinal epithelial cell function. Important chloride channels in the GI tract include the cystic fibrosis transmembrane conductance regulator (CFTR) channel

(single pore, cAMP regulated) and the CIC group (9 subtypes) of chloride channels (two pore, voltage dependent).

Lubiprostone, derived from a metabolite of PGE1, is a selective CIC-2 chloride channel activator [109]. CIC-2 channels are located on the apical cell membrane of human gastrointestinal cells and are found throughout the stomach, small intestine and colon (Figure 7). When CIC-2 channels are activated, there is an efflux of chloride through the channels into the gastrointestinal lumen. This causes the concomitant passage of sodium ions and water, via the paracellular pathway, in order to maintain electrical neutrality and isotonic equilibrium respectively. These actions add fluid to stool and promote increased gastrointestinal transit through stimulation of local receptors sensitive to stretch and distension.

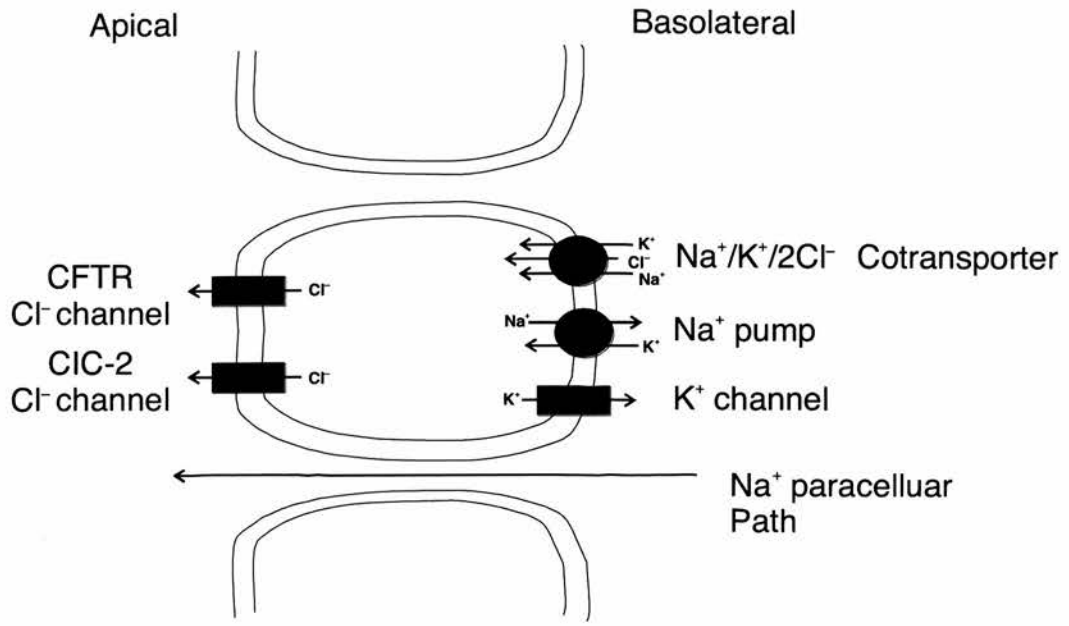

Figure 7 - *Intestinal expression of chloride channels.* *The CFTR and ClC-2 channels are located on the apical (luminal) side of the gastrointestinal epithelial cell. Although not a chloride channel, the Na+/K+/2Cl⁻ co-transporter is one of the major pathways for the movement of chloride from the bloodstream into the cell. This co-transporter is present on the basolateral (abluminal) cell membrane of intestinal epithelial cells.*

1.12.4 Behavioural modification and toilet training

Education is an important basis for the treatment of constipation. In order that children, and their parents, respond to treatment it is essential that they understand the commonness of their condition and are given plenty of reassurance and support. Habit training involves teaching a child to defecate regularly. Toileting programs should be developed in association with both the child and their parents in order to ensure maximum compliance. Ideally children should be encouraged to sit on the

toilet for 5-10 minutes after each meal. This takes advantage of the naturally occurring gastro-colic reflex. Children should be encouraged to keep a toileting diary with suitable praise for compliance, successful passage of a stool in the toilet and soiling free days. In addition, appropriate toileting posture and muscle co-ordination should be assessed and corrected by a trained physiotherapist [6 55]

Some children with FFR have abnormal defecation dynamics demonstrable by anorectal manometry. The most notable abnormality is paradoxical external anal sphincter contraction during attempted defecation (anismus) [110]. Biofeedback training aims to eliminate anismus by visually and aurally reinforcing repeated external anal sphincter relaxation until a recognisable sensation is achieved without the need for feedback. Although some studies have been encouraging [111-115] others have been unable to demonstrate any benefit [116-119].

1.13 Surgical management of constipation

Until recently surgical management of chronic treatment-resistant constipation consisted mostly of bowel resection with or without formation of a stoma [120-124]. Now, however, a less invasive approach is regularly being taken with the formation of a continent appendix stoma as first described by Malone for the management of incontinence associated with spina bifida [125-128]. The appendix is brought through the anterior abdominal wall, usually in either the right iliac fossa or at the umbilicus, and sutured to the skin to form an appendicostomy [125]. Antegrade continence enemas (ACE) are then performed via the stoma to flush faeces from the caecum to the rectum [125]. When the colon is intermittently (every 2-3 days) washed out in this

manner it remains relatively empty and continence and soiling are improved. Washouts can be performed via intermittent stomal catheterisation or via an indwelling device (Figure 8).

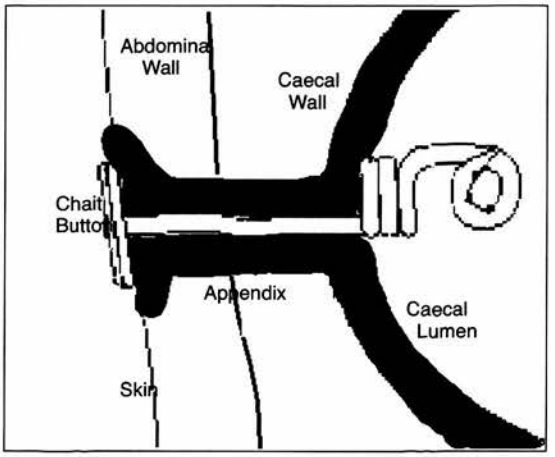

Figure 8 - *Chait button in appendix stoma* [128].

1.14 Complications

1.14.1 Disease related

Ineffective treatment can lead to faecal impaction that may require either medical or surgical disempaction. Constant soiling, if poorly managed, can result in perianal erythema and, in severe cases, excoriation [129].

1.14.2 Laxatives

There is widespread belief that chronic use of laxatives can lead to tolerance, habituation and even colonic damage and these misconceptions often lead to inappropriate prescribing practices. When used appropriately there are relatively few side effects to either bulk, osmotic or even stimulant laxatives [14].

1.14.3 Surgical

Intolerable stool leakage from an appendicostomy or stomal stenosis can both necessitate stomal revision [126].

1.14.4 Psychosocial

One of the biggest and least recognised complications of chronic constipation is the associated psychological insult. Chronic abdominal pain and constant faecal soiling can lead to disrupted peer relationships, undue family stress and social ostracism. Behavioural problems, which may be extreme, may be the cause in some patients, but more frequently are the result of years of living with constipation [130].

1.15 Evaluation of colonic transit

In order to determine what is abnormal in terms of colonic transit it is essential to understand what is normal. Several methods have been employed to assess gastrointestinal transit, with the most popular current techniques being radio-opaque marker and nuclear scintigraphic studies.

1.15.1 Radio-opaque marker studies

Radio-opaque marker studies involve the ingestion of plastic markers and subsequent tracking of their passage through the gastrointestinal tract. Their use is advocated in both adult and paediatric populations with several methods being described. Initially Hinton et al [131] described a technique that involved the ingestion of radio-opaque markers followed by x-ray of the stools until all markers were recovered. Following

this, practice changed with methods being introduced that followed the internal passage of the markers by process of serial abdominal radiograph. These techniques used a combination of bolus or repeated ingestion of markers paired with single or multiple radiographs. Arhan et al employed a technique that involved a single ingestion of markers followed by abdominal radiographs at 24-hr intervals until complete evacuation. This method was subsequently simplified by Metcalf et al [56] who administered subjects different-shaped markers on 3 consecutive days before performing a solitary abdominal radiograph on day 4. Although this method decreases radiographic exposure, it is felt that it underestimates colon transit time in patients with a transit time of greater than 72 hrs [60]. Most recently, Gutierrez et al [132] have described a technique that involves the ingestion of different shaped plastic markers for 6 days, with subsequent attainment of an abdominal radiograph on day 7. This method ensures that radiation exposure is low whilst maintaining the ability to assess both segmental and prolonged gastrointestinal transit.

1.15.2 Nuclear scintigraphy

Nuclear scintigraphy, or radioisotope gastrointestinal transit studies, have the ability to provide an accurate assessment of both global and segmental colonic transit time. Radiolabelled material is ingested (traditionally 99m-Technetium, 67-Gallium citrate or 111-Indium) and its passage through the gastrointestinal tract followed by the acquisition of sequential gamma camera images (see Figure 2, page 16). Taking multiple images (up to 5 days post ingestion of radioisotope) allows estimates of gastric emptying and both small bowel and regional colonic transit to be made [133]. Images can be assessed both by visual interpretation and by determining the

geometric centre (GC) of radioisotopic activity [134]. The gastrointestinal tract is divided into regions of interest (ROI) and each is given a number. Different studies divide the colon into varying numbers of ROI (between 4-99 are described [65 133 135-142] Figure 9). The geometric centre for any scintigraphic image is an objective figure, not a time in hours, and is dependent upon the number of regions of interest that the colon is divided into.

For each image, the fraction of administered activity in each ROI is multiplied by the region number (n) and then all are added to give the GC:

$$GC = \sum_{n}^{1} \text{fraction of activity in } ROI_n \times n$$

Studies can be reported in terms of total colonic or regional transit time (hrs) [143 144 137], GC at set time points (traditionally a combination of 6, 8, 24, 30, 48, 72 and 96 hrs) [65 133 135-142] or % of retained/excreted activity [135 141].

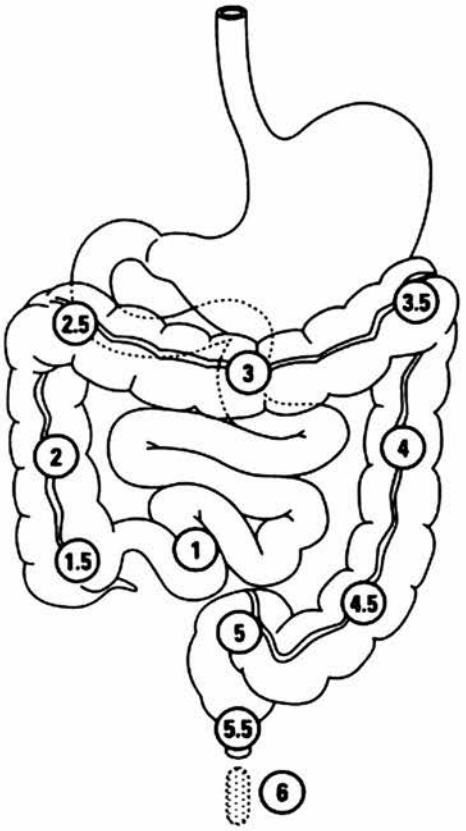

Figure 9 - *Colon is divided in 6 ROI (1 = Small bowel, 2 = Ascending colon, 3 = Transverse colon, 4 = Descending colon, 5 = Recto-sigmoid and 6 = Excreted)* [69].

A worked example for the calculation of the geometric centre of activity is shown in Figure 10. This figure represents a scintigraphic image taken at 6hrs. The radiolabelled material has reached the colon, but there is still some residual matter in the small bowel. 10% of measured activity remains within the small bowel (ROI = 1); 70% of activity is recorded in the ascending colon (ROI = 2) and the remaining 20% of activity has progressed into the transverse colon (ROI = 3). There is no activity in regions of interest 4-6). This gives the following calculation:

$$GC = (1 \times 0.1) + (2 \times 0.7) + (3 \times 0.2) + (4 \times 0) + (5 \times 0) + (6 \times 0)$$

$$= 0.1 + 1.4 + 0.6$$

$$= 2.1$$

Therefore it can be said for this example that at 6 hours, the geometric centre of activity is 2.1 i.e. the midpoint of radioactive activity is just beyond the midpoint of the ascending colon.

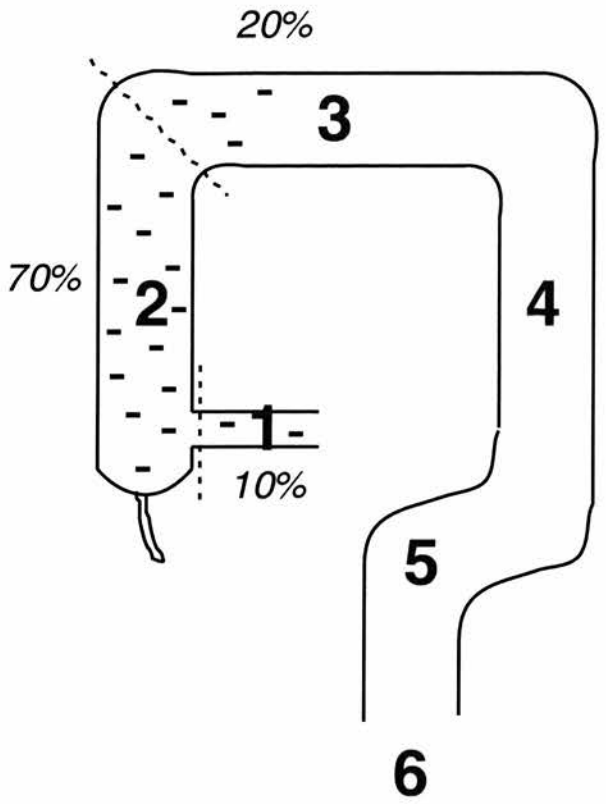

Figure 10 - *Worked example of calculation of GC of activity for scintigraphic image at 6hrs.* *Diagram represents colon with the regions of interest (ROI) - 1-6 - indicated. The percentage of total radiolabelled activity is shown (10, 70 and 20% in regions 1, 2 and 3 respectively).*

Although nuclear scintigraphy has been used in adults for some time, it has only been employed to assess gastrointestinal transit time in children since the late 1990's [69 143].

1.15.3 'Normal' colonic transit

Unfortunately there are no reports of normative data for children measured with scintigraphy with normal values of colonic transit time in children having to be either estimated from adult and paediatric plastic marker studies (Tables 7 and 8) or extrapolated from adult nuclear transit studies (Table 9). As studies have shown that marker studies appear to show similar transit rates in children and young adults [60 141 145-147], it is felt that it is reasonable to use scintigraphic data from adults to predict normative values in children and adolescents.

Table 7 - *Summary of review of studies evaluating colonic transit time in healthy paediatric controls employing either radio opaque marker techniques [148].*

Name	Population	Method	Findings
Zaslavsky et al [149] 1998	13 constipated children (9 male, 12-18 yrs) 13 healthy children (9 male, 12-18 yrs)	Radio-opaque marker (3 day ingestion), single x-ray (day 4)	Constipation - Total colonic transit time (TCTT) (mean ± SD) 58.3 ± 17.4 hrs (right colon 15.9 ± 12.4 hrs, left colon 14.7 ± 13.4 hrs, recto sigmoid colon 17.2 ± 16.2 hrs) Healthy - TCTT (mean ± SD) 30.2 ± 13.1 hrs (right colon 5.7 ± 3.9 hrs, left colon 7.9 ± 7.8 hrs, recto sigmoid colon 15.5 ± 10.6 hrs), upper limit of normal 56.6 hrs
Arhan et al [58] 1981	38 healthy adults, 23 healthy	Radio-opaque marker (single ingestion), x-	Adult mean TCTT 38.9 hrs (right colon 13.8 hrs, left colon 14.1 hrs, recto sigmoid colon

	children (all less than 15yrs); 32 males (total study group)	ray every 24hrs until complete evacuation	11hrs), upper limit of normal (mean ± SD) 93 hrs Child mean TCTT 28.8 hrs (right colon 7.7 hrs, left colon 8.7 hrs, recto sigmoid colon 12.4 hrs), upper limit of normal (mean ± SD) 62 hrs
Wagener et al [60] 2004	22 healthy children (median age 10 yrs, 4-15 yrs)	Radio-opaque marker (6 day ingestion) single x-ray (day 7)	Mean TCTT 39.6 hrs (7.2-86.4 hrs, "upper limit of normal" (95th percentile) 84 hrs) Mean ascending colonic transit time (CTT) 5.5 hrs (0-14.4 hrs, 95th percentile 14.2 hrs) Mean transverse CTT 10.9 hrs (0-33.6 hrs, 95th percentile 33.1 hrs) Mean descending CTT 6.1 hrs (0-21.6 hrs, 95th percentile 20.6 hrs) Mean recto sigmoid CTT 18.2 hrs (0-40.8 hrs, 95th percentile 40.8 hrs)
Corraziari et al [150] 1985	25 healthy children (2/12-12 yrs)	Radio-opaque marker (single ingestion) faecal x-ray until 80% eliminated	TCTT (mean ± SD) 25.0 ± 3.7 hrs, upper limit of normal (mean + 2 SD) 32.4 hrs
Gutierrez et al [132] 2002	30 healthy children (2-14 yrs)	Radio-opaque marker (6 day ingestion) single x-ray (day 7)	TCTT (mean ± SD) 29.08 ± 8.3 hrs (right colon 7.25 ± 5.75 hrs, left colon 6.6 ± 6.2 hrs, recto sigmoid colon 14.96 ± 8.7 hrs), upper limit of normal (mean + 2 SD) 45.68 hrs
Bautista Casasnovas et al [151] 1991	14 constipated children, 10 healthy children (6-14 yrs)	Radio-opaque marker (3 day ingestion) daily abdominal and faecal x-ray + single x-ray (day 4)	Constipated - TCTT (mean ± SD) 59.9 ± 5.4 hrs (right colon 15.9 ± 2.3 hrs, left colon 18.9 ± 2.3 hrs, recto sigmoid colon 25.0 ± 2.6 hrs) Healthy - TCTT (mean ± SD) 37.8 ± 6.2 hrs (right colon 10.8 ± 3.5 hrs, left colon 12.2 ± 2.7 hrs, recto sigmoid colon 14.7 ± 2.1 hrs), upper limit of normal (mean + 2 SD) 50.2 hrs

As all of the studies employ widely different methods to both carry out and report their investigations, ascertaining what indeed construes 'normal' colonic transit is a somewhat difficult task. When looking at the studies that have used radio-opaque markers to assess colonic transit in normal children [58 60 132 149-151], mean total colonic transit time (TCTT) is reported as being from 25 ± 3.7 hrs (mean ± SD) [150] to 39.6 hrs (mean, range 7.2-86.4 hrs) [60] with upper limits of normal described as being anywhere between 32.4 hrs [150] and 84 hrs [60]. Similar diversity is seen when looking at the corresponding adult plastic marker studies [56 58 131 152 153]. When reviewing the scintigraphic studies, it is very difficult to apply the findings to a normative population. Studies that report transit in terms of GC do not provide one with a quantitative time value for 'normal' colonic transit; therefore, unless one is using the same protocol, with the same number of ROI, the values are somewhat meaningless. Those studies that do report in terms of mean colonic transit time [137 143 144] describe normal values of between 22.3 ± 4.8 hrs (mean ± SD) [143] and 41.1 (range 14-80 hrs) [144].

Table 8 - *Summary of review of studies evaluating colonic transit time in healthy adult controls employing radio opaque marker techniques*[148].

Name	Population	Method	Findings
Cucchiara et al [153] 1984	53 constipated adults (40 male, mean age 8.3 yrs) 46 healthy adults (24 male, mean age 8.1 yrs)	Radio-opaque marker (single ingestion), faecal x-ray until 80% eliminated	Constipation (+ faecal soiling) – Gastrointestinal transit time (GITT) (mean ± SD) 58 ±14.3hr (range 36-86 hrs) Constipation (– faecal soiling) - GITT (mean ± SD) 61.1 ± 15 hr (range 36-96 hrs) Healthy GITT (mean ± SD) 25.6 ±3.7 hr (range 19-33 hrs)
Chaussade et al [152] 1986	22 healthy adults with bran enriched diet	Radio-opaque marker (3 day ingestion) x-ray (day 4 and 7)	TCTT (mean ± SD) 34.4 ± 16.2hrs (right colon 6.9 ± 7.8 hrs, left colon 9.1 ± 10.3 hrs, recto sigmoid colon 18.4 ± 12.5 hrs)
Arhan et al [58] 1981	38 healthy adults, 23 healthy children (all less than 15yrs); 32 males (total study group)	Radio-opaque marker (single ingestion), x-ray every 24hrs until complete evacuation	Adult mean TCTT 38.9 hrs (right colon 13.8 hrs, left colon 14.1 hrs, recto sigmoid colon 11hrs) Child mean TCTT 28.8 hrs (right colon 7.7 hrs, left colon 8.7 hrs, recto sigmoid colon 12.4 hrs), upper limit of normal (mean + 2 SD) 62 hrs
Metcalf et al [56] 1986	24 healthy adults (10 male)	Radio-opaque marker (3 day ingestion) daily abdominal and faecal x-ray + single x-ray (day 4)	TCTT (mean ± SE) 35.0 ± 2.1 hrs (right colon 11.3 ± 1.1 hrs, left colon 11.4 ± 1.4 hrs, recto sigmoid colon 12.4 ± 1.1 hrs)
Hinton et al [131] 1969	25 healthy adults (25 male, 18-40 yrs)	Radio opaque marker (single ingestion) faecal x-ray until 80% eliminated	All subjects passed first marker within 66hrs, all except one passed 80% within 114 hrs

Table 9 - *Summary of review of studies evaluating colonic transit time in healthy adult controls employing nuclear scintigraphic techniques*[148].

Name	Population	Method	Findings
Lundin et al [133] 2004	23 constipated adults (19 female, mean age 50 yrs) 15 healthy adults (11 female, mean age 46 yrs)	Scintigraphy (111-Indium) Images @ 6, 24, 48 and 72 hrs (ROI 1-8) GC + % activity over time (%AOT)	Healthy - mean GC @ 6hrs - 2; 24hrs - 3.5; 48hrs - 5 and 72hrs - 6.5 Constipation cf. healthy - No difference in right sided transit, significant delay in patients in left sided transit
Krevsky et al [135]1986	7 healthy children (7 male, mean age 24.9 yrs)	Scintigraphy (111-Indium directly instilled into caecum) GC (ROI 1-7) + % AOT	By 48 hrs, 70.7% ± 9.1% (mean ± SEM) had been excreted. Rapid emptying of caecum and ascending colon - half emptying time of 87.6 ± 27.9 min
Tota et al [143] 1998	15 healthy adults (9 male, mean age 8.5 yrs)	Scintigraphy (111-Indium) Images @ 6, 24, 30, 48, 54 and 72 hrs	TCTT (mean ± SD) 22.3 ± 4.8 hrs (right colon 5.4 ± 3.0 hrs, left colon 7.1 ± 3.4 hrs, recto sigmoid colon 9.8 ± 3.2 hrs)
Park et al [136] 2006	11 healthy adults (5 male, mean age 39.9 yrs)	Scintigraphy (99m-Technetium) Images @ 6, 8 and 24 hrs (5 ROI)	Colonic filling @ 6hrs (mean ± SE) - 44 ± 8 %; GC @ 8 hrs - 1.4 ± 0.1 and 24 hrs - 2.6 ± 0.3
Kamm et al [154] 1988	6 healthy adults (4 male, all 23 yrs) 7 constipated adults (1 male, 26-51 yrs)	Scintigraphy (99m-Technetium; direct colonic intubation + bisacodyl) Scanning until bulk of isotope in rectum	No movement of isotope over 10-15 mins until bisacodyl introduced Healthy - hepatic flexure to rectum time 1-10 mins (mean 5.3 mins) Constipated - hepatic flexure to rectum time 14-25 mins with no movement at 2 hrs in 2 patients
Stubbs et al [137] 1991	10 healthy adults (mean age 26 yrs)	Scintigraphy (111-Indium) Images at 3-6 hrs, then every 4 hrs until 72hrs (5 ROI)	Mouth to caecum (mean ± SD) - 5.4 ± 2.2 hrs Caecum to hepatic flexure - 5.3 ± 3.7 hrs Caecum to splenic flexure - 12.1 ± 8.2 hrs Caecum to recto sigmoid - 19.6 ± 12.0 hrs

			Caecum to excretion - 31.2 ± 16.3 hrs
Cremonini et al [138] 2002	37 healthy adults (10 female, mean age 39 years)	Scintigraphy (111-Indium) Images @ 0, 1, 2, 4, 6, 24 and 48 hrs (4 ROI)	Colonic filling @ 6hrs (mean ± SEM) - 71 ± 5 %; GC @ 24 hrs - 2.67 ± 1.09 and 48 hrs - 3.89 ± 0.15 hrs
Roberts et al [140] 1993	16 healthy adults (12 female, mean age 28 yrs)	Scintigraphy (111-Indium) Images at 18 - 72 hrs (7 ROI)	GC @ 24 hrs (lower and upper 95% confidence intervals) - 1.97-6.76, 48hrs - 3.6-7.0 and 72 hrs - 6.26-7.0
Eising et al [65] 1998	22 healthy adults	Scintigraphy (111-Indium) Images @ 8, 24 and 48 hrs (5 ROI)	GC @ 8 hrs (mean) - 1.48, 24 hrs - 2.83 and 48 hrs - 4.07
Krevsky et al [139] 1992	15 healthy adults (15 male, mean age 29.3 yrs)	Scintigraphy (111-Indium) Images @ 24 and 48 hrs (10 ROI)	GC @ 24 hrs (mean ± SEM) - 4.24 ± 0.53 and 48 hrs - 6.22 ± 0.22
Proano et al [141] 1990	14 healthy adults (8 male, mean age 31.5 yrs)	Scintigraphy (111-Indium) Images @ 0-2, 24, 48 and 72 hrs (4 ROI)	% distribution @ 24 hrs (mean ± SE): ascending colon - 22 ± 7, transverse colon - 34 ± 8, descending colon - 7 ± 2, rectosigmoid colon - 5 ± 3, stool - 32 ± 10 % distribution @ 48 hrs (mean ± SE): ascending colon - 5 ± 2, transverse colon - 30 ± 10, descending colon - 4 ± 2, rectosigmoid colon - 3 ± 1, stool - 56 ± 11
McLean et al [142] 1992	41 healthy adults (22 female, mean age 41.5 yrs)	Scintigraphy (111-Indium) Images @ 24, 48, 72 and 96 hrs (99 ROI)	Mean activity position of isotope @ 24 hrs - 68.4 (F), 84.5 (M); 48 hrs - 94.7 (F), 96.7 (M); 72 hrs - 98.5 (F), 98.1 (M) and 96 hrs - 98.9 (F), 98.7 (M)
Graff et al [144] 2001	32 healthy adults (16 male, 22-53 yrs)	Scintigraphy (111-Indium) Images at 24hr intervals until all activity cleared	Colonic mean transit time - 41.1 (range 14.0-80.0) hrs

1.15.4 Abnormal colonic transit

Beninga et al [19] set a value of CTT >100 hrs for the definition of children with STC based on the upper limit (mean + 2 SD) from the work of Corazziari et al [150]. Although this study contains data from non-constipated subjects, this arbitrary figure is derived from the upper limit of total gastrointestinal transit time (TGITT) (not in fact CTT as Beninga states) of a subset of children with constipation and a TGITT > 33hrs. By deriving a value for slow colonic transit in this manner, Beninga provides an inflated estimate of what is likely to be truly abnormal [19].

When colonic transit is assessed by scintigraphic methods, rather than an arbitrary figure being applied as to what constitutes delayed total transit, a more detailed picture of regional transit can be formed [69]. By determining the distribution of activity at 48hrs, children can be divided into those with right sided and transverse colonic retention (i.e. true STC) and those in whom the delay occurs at the retosigmoid junction (FFR) [69].

1.16 Evaluation of colonic motility

In the past, colonic motility has remained largely unevaluated due both to the relative inaccessibility of the colon and the lack of an appropriate animal model. Unlike most animals, the human colon does not exhibit a cyclical, easily recognisable motor pattern which adds to the difficulty in interpretation of colonic motor activity [155].

1.16.1 Normal colonic motility (in adults)

The interdigestive pattern of motor activity seen in the upper gastrointestinal tract does not occur in the colon. Instead, non-cyclical motor activity is exhibited consisting of quiescent periods sporadically interspersed with non-propagating and propagating contractions, producing an irregular passage of colonic luminal contents [155]. Contractions can be defined as being either *tonic* or *phasic*. Tonic contractions last more than 30 seconds and often have the shorter phasic contractions superimposed on them. Contractions can be in either an aboral (antegrade) or oral (retrograde) direction, producing a mixing of colonic contents and allowing adequate absorption of water and electrolytes [155].

High amplitude propagating sequences (HAPS) are a feature of normal colonic motility. HAPS are defined as colonic propagating sequences where the amplitude in at least one recording channel exceeds 116mmHg [76 155] As with normal propagating sequences, HAPS can occur in either an antegrade or retrograde (high amplitude retrograde propagating sequence - HARPS) direction, although HARPS are thought to rarely occur in states of health. HAPS have been found to originate most commonly in the proximal colon with associated distal propagation. It is not clear what initiates them, however most HAPS are associated with colonic mass movement including the passage of faeces or wind [155]. An increased frequency of HAPS is seen in the post-prandial period and following waking [76]. Direct colonic instillation of Bisacodyl has the ability to induce HAPS identical in terms of amplitude, length of propagation and velocity to those seen in normal physiological states; its mechanism of action is poorly understood [156].

Different studies report differing expected frequencies of HAPS in 'normal' adults ranging from 2 per 24 hrs [157] up to 10 per 24 hrs [155]. These differences can be explained by widely dissimilar study protocols involving a variation of: recording catheter (solid vs. water perfused), bowel cleansing (preparation vs. no preparation), length of recording (6 hrs up to 24 hrs), catheter position (proximal caecal vs. distal rectosigmoidal recording) definition of HAPS (>80mmHg [77] [158] - >200mmHg [159]) patient position (recumbent vs. ambulatory) and data interpretation (visual vs. automated).

Some colonic cyclic activity does exist in the region distal to the rectosigmoid junction, however it is not related to the cyclical activity displayed in the upper intestine [160]. It is described as the rectal motor complex (RMC) and is part of normal colonic motility in adults. 3 patterns of cyclical rectal activity have been observed [160]: (i) runs of powerful phasic contractions with a frequency of 2-3/minute, lasting for 3-10 minutes and recurring at an interval of 92 ± 1.9 (mean ± SEM) minutes during the day and 56 ± 1.7 (mean ± SEM) minutes during the night; (ii) isolated prolonged contractions lasting for 10-20 seconds and seen mainly during waking; and (iii) clusters of contractions occurring at a frequency of 5-6/minute lasting for 1-2 minutes and seen predominantly during the post-prandial period. The physiological role of the RMC remains unknown [160].

Since, apart from obvious propagating sequences and the RMC, colonic activity often does not represent any obvious motility pattern, motor activity is also quantitatively described in terms of a motility index (MI). This involves measuring

the activity under the curve from pressure tracings. In this way, colonic motor responses to physiological stimuli such as eating and waking can be more accurately evaluated [155].

It is normal in adults to see an increase in the motility index after eating - the so called gastrocolonic reflex [161]. An increase in colonic activity is seen within 20-40 minutes of commencing eating with late and early components occurring at 20 and 60 minutes respectively. This response is most prominent in the distal colon [162] and its magnitude is proportional to the fat contents of the ingested food, with a higher content evoking an increased response [163]. In controlled circumstances, a fat content of >40%/meal is used to stimulate this colonic response to food.

1.16.2 Child vs. adult normal motility

Due to obvious ethical considerations, the majority of colonic manometric recordings from children are of a short duration, only involve the lower, more accessible, colon and have been performed on abnormal colons [77 158]. A lot of what is 'known' about paediatric colonic motility has been extrapolated from adult studies and there is subsequently a variation is what is currently perceived as both 'normal' and 'abnormal' [76 77 158].

Like their adult counterparts, children demonstrate increased colonic motility in response to eating and waking however, their post-prandial response is more rapid, shorter lasting and characterised mainly by an increased frequency of HAPS [77 158]. In addition, children are thought to have more frequent HAPS than adults and which are

more often associated with the urge to defecate or an act of defecation. Children also exhibit a diurnal variation in colonic activity with a decrease in motor activity seen during sleep.

1.16.3 Abnormal colonic motility associated with STC

Both adults and children with STC have been shown to exhibit a lower frequency of antegrade propagating sequences [76 77 158 164] and lack the degree of response to eating and waking seen in states of health. There is however much debate as to the ability of both adults and children with STC to generate HAPS. Some centres believe a lack of normal physiological HAPS in combination with an absence of HAPS in response to colonic instillation of Bisacodyl to be a diagnostic feature of subjects with STC [77 158]. Other centres have recorded HAPS in both adult [164] and paediatric [76] STC colons. These studies have found that although some subjects with STC appear to possess the ability to generate high pressure activity, the frequency of such events (as with the low pressure propagating sequences) is significantly decreased. This degree of diversity in the manometric findings can be attributed to either different study protocols or different diagnostic criteria for STC (based on radiological investigations) or may reflect the fact that subjects with STC represent an as yet unrecognised heterogeneous group of colonic pathologies.

1.17 Summary

Constipation is a common childhood condition with a spectrum of severity that ranges from solitary, self-limiting attacks of 'acute' constipation through to long-standing, treatment-resistant chronic constipation. Although the majority of children

will respond to conventional management, there are some for whom constipation represents a debilitating condition that is unresponsive to current therapy. Although the cause of their constipation remains unknown, it is now widely believed that their disease may have a hidden or unrecognised organic origin and that they may have a variety of underlying pathologies that produce a similar clinical picture.

It is important to identify this group of children, through appropriate investigations, in order to attempt to meet their needs and provide them with appropriate support and treatment. Novel diagnostic techniques, such as nuclear transit studies and colonic manometry, are no longer being considered as purely research tools and are becoming more widely available and more commonly accepted as standard practice. By employing such techniques as part of routine clinical work-up, children with abnormal colonic motility can be identified and diagnosed early in their clinical course before true chronicity is established.

2. Electrical Stimulation as a Treatment Modality for Gastrointestinal Disorders

2. Electrical Stimulation as a Treatment Modality for Gastrointestinal Disorders

2.1 Introduction

Scientific enquiry into the phenomena known as magnetism and electricity is centuries old. Many have dedicated their life's work to expounding the effects and potential applications. The time and place of their discovery, and indeed their first therapeutic use, remain unknown, however historical literature is scattered with colourful accounts of their existence. Throughout the Middle Ages it was believed that magnets had wondrous powers: they were used to cure baldness, to purify wounds, to treat gout and arthritis, and were even thought to have aphrodisiacal qualities!

In 1743, Johann Gottlob Kruger (1715-1759) suggested that electric current could induce changes in the body that would restore or maintain health [165]. He based this principle on the fact that the application of an electrical current seemed to increase the blood flow to the area. Around the same time, Benjamin Franklin (1706-1790) [166] as part of his studies into the application of electricity, began treating paralysed patients with thrice-daily shocks to their affected extremities. He found that although the patients' limbs seemed to strengthen somewhat, the sessions were painful and the benefits were short-lived.

In 1760, possibly inspired by Franklin's work, John Wesley (1704-1791) [167], an English clergyman, established free medical clinics in Bristol and London and offered electrification in the belief that it could be used to treat a number of ailments

(Table 10). This concept of electrotherapy was further explored by Guillaume Benjamin Amand Duchenne (1806-1875), the French neurologist, in the 1800's [168]. He developed his use of faradism (the application of a faradic current of electricity for therapeutic or diagnostic purposes) by building his own electrical box-like machine (Figure 11). He regularly carried this with him on his rounds, using it to stimulate the muscles and nerves of his patients (Figure 12). Duchenne was the first to describe several nervous and muscular disorders and to suggest possible electrically modulated therapeutic options.

Table 10 - The Desideratum, or Electricity made Plain and Useful by a Lover of Mankind and of Common Sense [168].

Disorders in Which Wesley Thought Electrification to be of Use	
Agues	King's Evil
St. Anthony's Fire	Knots in the Flesh
Blindness, even from a Gurra Serena	Lameness, Leprosy
Blood extravasated	Mortification (dead flesh)
Bronchocele	Palpitation of the Heart
Chlorosis	Pain in the back, in the Stomach
Coldness in the feet	Palsy, Pleurisy
Consumption	Rheumanism, Ring worms
Contractions of the limbs	Sciatica, Shingles, Sprain
Cramp	Surfeit (excessive eating)
Deafness, Dropsy	Swellings of all kinds
Epilepsy	Throat sore
Feet violently disorded	Toe hurt
Felons	Tooth - Ache
Fistula Lacrymalis	Wen (tumor on the scalp)
Fits	
Ganglions	
Goitre	
Gout	
Gravel	
Head ache	
Hysterics	
Inflammations	

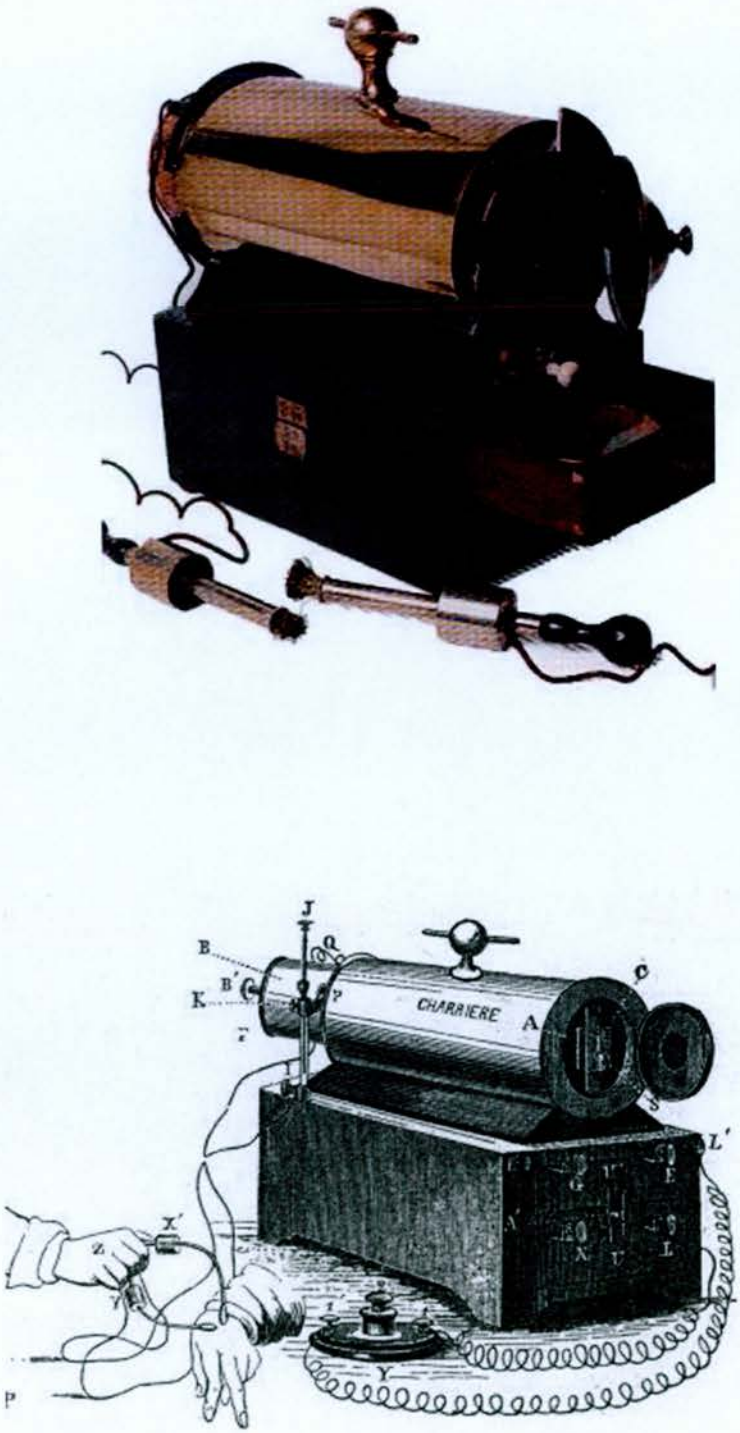

Figure 11 - *Electrisation apparatuses used by Dr. Duchenne* [168].

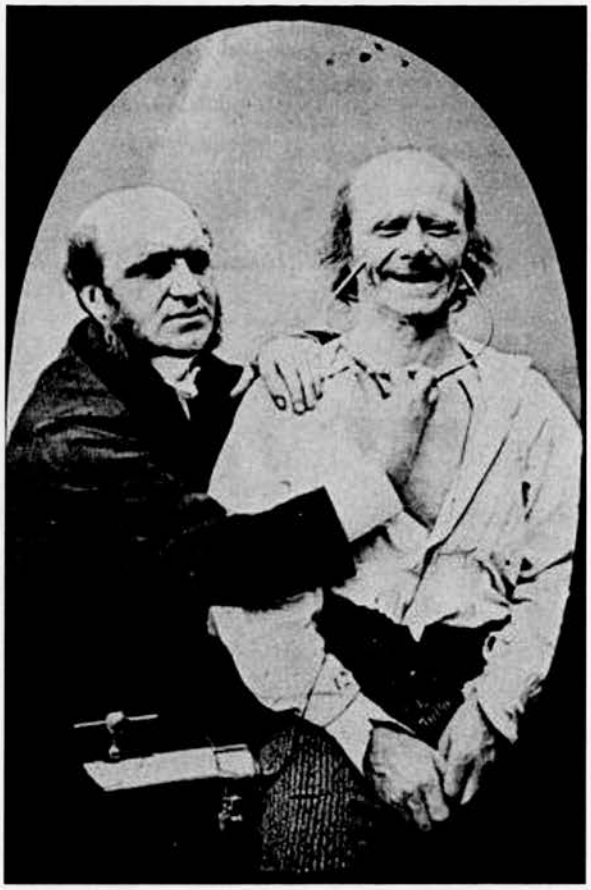

Figure 12 - *Self-portrait of Dr. G.B. Duchenne using his electrisation apparatus, 1862* [168].

By the mid nineteenth century, the use of electrical devices had become popular throughout Europe and the United States.

Over the past century the popularity of electrical therapy has fluctuated immensely. Although there are many who believe in the benefit of its clinical application, there remain those who are unconvinced as to its clinical value. A lot of the scepticism is related to the ambiguity concerning the proposed mechanisms of action involved in the application of any type of electrical therapy. Many theories have evolved over

the years as to the potential effects of electrical stimulation on human tissues, but in truth they remain speculations rather than facts.

2.2 Types of electrical stimulation

2.2.1 Transcutaneous Electrical Nerve Stimulation (TENS)

There currently exist several types of electrical therapy that differ both in their use of current and their mode of delivery. Most people are familiar with the concept of Transcutaneous Electrical Nerve Stimulation or TENS, as it is more popularly known [169]. TENS was initially used in the 1960's and introduced into clinical practice the concept that pain may be relieved by peripheral stimulation that can take the form of rubbing, vibration, heat, cold or, in the case of TENS, electrical stimulation. The electric stimulus is delivered at variable current strengths, pulse rates and pulse widths. The waveform is biphasic in order to avoid the electrolytic and iontophoretic effects of a unidirectional current. TENS is traditionally categorised into 3 forms [169]: high-frequency, low-frequency and pulsed (burst). The most conventional form of TENS is high-frequency. The stimulus is delivered at a frequency >10Hz (usually 40-150Hz) but at a low current intensity, between 10-30mA, which is below a level producing pain. The pulse duration is short, typically around 50 microseconds. Low-frequency TENS delivers a stimulus of <10Hz (usually 1-10Hz), at a high current intensity, close to the tolerance limit of the patient. It is often uncomfortable and many patients cannot tolerate it. Pulsed TENS, uses low-intensity stimuli fired in high-frequency bursts. No particular advantage of this method over conventional TENS has been described [169].

2.2.2 Interferential therapy (IFT)

Interferential therapy (IFT) is a form of electrical stimulation that involves the transcutaneous application, via electrodes, of two crossed, slightly out of phase, medium-frequency currents. This produces an amplitude-modulated current effect within the tissues [170]. As with TENS, the frequency, amplitude and pulse width of the output waveforms can be regulated. Conventionally, currents within the range of 3,900 to 4,100Hz are used, as lower frequency currents can result in somewhat uncomfortable polarisation effects in the superficial tissues [171]. Typically a quadripolar model is adopted where four electrodes are placed over the target area in such a distribution that their current paths cross directly over the relevant organ(s).

2.2.3 Electroacupuncture

Although the Chinese have been using acupuncture for the around the last 3000 years, it wasn't until the 17th century that it was introduced to Europe. Even then it failed to gain popularity in Western culture with the majority of people regarding it as Eastern folklore. It is only in the last 25 years that there has been a dramatic turn around in the perceived acceptability of acupuncture. This follows the publication of long-awaited articles that finally reveal causal mechanisms for many of acupuncture's effects [172].

Ulett et al [173], observed that Chinese surgeons often added electricity via the needles in cases where they required a higher level of analgesia. They studied experimentally induced pain toleration in healthy volunteers and found that although acupuncture with needles alone gave some pain relief, when electricity was added the

modulation was 100% more effective. Han et al [174] have demonstrated a differential release of brain neuropeptides by different frequencies of stimulation.

2.2.4 Sacral Nerve Stimulation (SNS)

Sacral nerve stimulation (SNS) was first proposed in 1906 for the treatment of micturition disorders. Initially therapy took the form of transcutaneous stimulation before development of devices that employed transvaginal [175] and transrectal routes [176]. Unfortunately these devices were prone to infection, migration or fibrous tissue reaction and so did not gain the popularity that was initially expected. More recently a new form of stimulation has been created that involves extradural stimulation within the sacral canal and is primarily utilised in the management of faecal incontinence [177-179]. Following acute peripheral nerve evaluation to locate the optimal sacral spinal nerve that will elicit contractions of the striated pelvic floor muscles (usually S3), patients progress to subchronic peripheral nerve evaluation for a minimum of 7 days to assess the relative efficacy of SNS. If a clear benefit is perceived then a permanent implantable device can be inserted. Adoption of this route of administration of electrical therapy has dramatically reduced the incidence of complications and this had lead to a more widespread adoption of SNS [177-179].

2.3 The passage of electrical current through live tissue

Transcutaneous electrical therapy is delivered by means of electrodes that are placed directly onto the recipient's skin. These are either applied to the area overlying the target organ or over the root of the affected dermatome or appropriate acupuncture sites. The electrodes and/or skin are coated in a conductive gel in order to minimise

contact resistance to the current flow and decrease energy losses in the form of heat or capacitive effects. In order to lower the current density flowing through the skin, it is important to maximise the surface area of contact. High current densities result in localised pain and inflammation [180]. Electrodes must be placed at least a few centimetres apart in order to prevent short-circuits from forming.

Typically, human tissue is anisotropic, non-linear and inhomogeneous meaning that it has properties that differ according to the direction of measurement [181]. Although a few studies have attempted to ascertain the relative distribution of current when applied to live tissue [182-185], very little information has been gathered due to the complex composition of human tissue, the immense variability between subjects and the technical difficulties in obtaining *in vivo* measurements. Consequently, scanty data concerning the precise nature of tissue impedance exist. Lerman *et al* [182] whilst investigating the intrathoracic passage of defibrillation current found that only 4% of transthoracically applied current actually reaches the target organ of the heart.

The mapping of electrical currents and other electromagnetic waves inside the human body requires the application of complex mathematical models. Most set-ups incorporate detailed computer-aided design software packages in an attempt to simulate *in vivo* conditions, however there is still some doubt as to the accuracy of their ability to predict live tissue current flow. Currently, the finite element analysis (FEA) model is most commonly utilised in situations where researchers are attempting to ascertain the supposed passage of various electrical currents [186]. This method of analysis converts a continuous solution domain into a finite "mesh" of

uniform and non-uniform elements that are connected via nodes. This mesh is programmed to represent the material and structural properties of human tissue which then defines how it will react to certain loading conditions or the application of current. The value of particular electrical quantities at a specific node can be calculated by applying difference equations based on the existing values of adjacent nodes. In this way the FEA provides the ability to model the complex tissue properties found in living matter [187].

2.4 The application of electrical stimulation in the treatment of gastrointestinal disorders

Electrical therapy has been applied in the management of a wide range of gastrointestinal disorders. By utilising different modes of delivery, electrical stimulation has been used in the treatment of many gastrointestinal motility disorders (achalasia, delayed gastric emptying, irritable bowel syndrome, constipation, faecal incontinence) as well as oesophageal visceral pain and severe functional abdominal pain.

2.5 The proposed action of TENS on the upper gastrointestinal tract

It is widely appreciated that gastrointestinal motility is controlled by an intrinsic electrical rhythm that is modulated by the parasympathetic, sympathetic and enteric nervous systems and gastrointestinal hormones. It is believed that the effect of TENS on the gastrointestinal tract must involve actions in addition to the gate theory mechanism [188]. It has been hypothesised that TENS could affect gastric motility by an action on cardiac nerves and the subsequent release of peptides [189]. It is thought

that the primary peptide involved in this pathway is VIP, however it is possible that TENS may stimulate the release of other neurotransmitters contained in VIPergic neurons (peptide histidine isoleucine (PHI), neuropeptide Y (NPY) and galanin) [189].

In some studies aiming to stimulate the upper GI tract, TENS is applied to the hand. The hand contains recognised gastrointestinal acupuncture points. One electrode (negative) is placed between the first and second metacarpal bones, and the other (positive) at the ulnar border of the hand [190]. This set-up is designed to stimulate dermatomes C8-T1 and elicit centrally relaying somatovisceral reflexes. One study compared the effect of TENS on the upper GI tract when applied to either the hand or foot [190]. It found that there was a measurable effect when TENS was applied to the hand but no effect when applied to the foot. They concluded that this provided strong evidence for the existence of a somatovisceral pathway.

Camilleri et al [191] applied TENS to volunteers while simultaneously monitoring their upper gastrointestinal phasic pressure activity, extraintestinal vasomotor indices, and plasma levels of accepted humoral mediators of autonomic reflexes. Stimuli were applied either to the hand (C8-T1) or to the upper abdomen (T5-T10) to determine whether impulses at these two dermatomes produced different effects. They noted a significant reduction ($p = 0.007$) in the antral motility index when TENS was applied to the hand and abdomen as compared with sham stimulation. They also describes an associated increase in skin conductance and plasma beta-endorphin levels but no change in pulse, blood pressure, or circulating catecholamine levels. They concluded that the similarity of the responses to TENS applied to the hand and

abdominal dermatomes suggested that the induced somatovisceral responses relay predominantly at the cerebral level.

2.6 TENS and achalasia

Achalasia is a disorder of the oesophagus in which there is a failure of the lower oesophageal sphincter (LOS) to relax during swallowing. In addition there is an abnormality in oesophageal motility and a high resting pressure of the LOS. VIP is believed to be the inhibitory neurotransmitter responsible for relaxation of the LOS. In patients with achalasia, the concentration of VIP and the number of VIP-containing nerve fibres are reduced or absent. The application of TENS as a treatment modality in patients with achalasia has been assessed in a number of trials [190] [192-194]. High or low frequency TENS is applied to the subjects' hand until rhythmic flexion of the fingers is obtained without producing pain.

In one study involving patients with achalasia, the pressure of their LOS, along with their VIP levels, were measured before and after treatment [193]. The authors reported that there was a statistically significant reduction in the LOS pressure after only 45 minutes of treatment at low-frequency (6.5Hz). This reduction was further increased after a week of daily treatment. They hypothesised that this response may be mediated by a nonadrenergic noncholinergic pathway of the autonomic nervous system and reported a 30% increase in VIP levels following TENS treatment. In contrast another study, that looked at oesophageal motility and LOS pressure in patients with achalasia and scleroderma [194], reported that there was no detectable

changes in oesophageal motility following administration of either low or high frequency TENS.

2.7 Electrotherapy for delayed gastric emptying

It is generally accepted that gastric electrical activity plays an important role in the control of gastric motor activity. Gastric myoelectrical activity can be measured by cutaneous electrogastrography (EGG) and abnormal recordings have been reported in a number of conditions including diabetic gastroparesis, pregnancy induced nausea and vomiting, motion sickness, chronic intestinal pseudo-obstruction and anorexia nervosa [195]. Allegedly, all of the above conditions have been successfully treated by means of acupuncture, electroacupuncture or acupoint TENS with success possibly resulting from an alteration in gastric electrical activity [196]. In order to confirm or dispute this, Chang et al [196] examined if electrical stimulation over Zusanli points in healthy volunteers produced any demonstrable changes in myoelectrical EGG recordings. The Zuslani point (also known as 'stomach-36') is one of the 365 recognised classical acupuncture sites and is one of the most frequently used. It is located on the anterolateral aspect of the lower leg, approximately 1 finger's breadth below the tibial tuberosity. The study showed that electrical stimulation appeared to provoke a significant increase in the percentage of normal frequency gastric electrical activity with concomitant decreases in the percentages of periods of tachygastric and bradygastric rhythms [196]. These findings lead the authors to the conclusion that transcutaneous Zusanli electrical stimulation has the ability to enhance the regularity of gastric myoelectrical activity. These findings supported the earlier work of Lin et al [197].

Weinkauf et al [198] describe two case reports of patients with post-lung-transplant gastroparesis due to a presumed vagus nerve injury during their operations. The first patient, who was receiving TENS for back pain, was noticed to have a marked improvement in his gastric emptying following his electrical therapy. The authors proceeded to apply paraspinal TENS to another patient with persistent gastroparesis some 8 months post-transplant. After a treatment period of 20-30 days her symptoms had also completely resolved.

2.8 TENS and severe functional abdominal pain

A small, uncontrolled study in 1986 looked at the effects of TENS on a population of patients with intractable "functional" abdominal pain [199]. This is a condition defined as abdominal pain for which no structural, biochemical or infective cause can be determined. Twenty-nine patients were given high frequency TENS stimulation (30-100Hz) for a treatment period of at least one month. The electrodes were initially placed over the site of pain; however, if there was no perceived effect, other electrode positions were tried. This meant that the electrodes were then placed either paraspinally (over the root of the affected dermatome) or over appropriate acupuncture sites. 21 of the 29 patients reported some benefit from the TENS after one month of treatment with the effect being maintained at six months in 15 patients. Of those who reported an initial response to treatment, 17 responded to placement of electrodes over the abdomen, 5 to placement paraspinally, and 2 to placement over acupuncture points (3 patients responded at more than one site). The authors concluded that TENS may provide pain relief in some patients with functional

abdominal pain and although the response could have been a placebo effect, the maintenance of symptom relief made this unlikely.

2.9 TENS and irritable bowel syndrome

Irritable bowel syndrome (IBS) is defined as a condition that is characterised by lower abdominal pain in association with disturbed defecation in the absence of any organic abnormality. Those diagnosed with IBS can be further classified as having either diarrhoea-predominant IBS (IBS-D) or constipation-predominant IBS (IBS-C) [200]. Currently the most widely accepted physio-pathological hypothesis to explain IBS is the presence of dysregulation of the neurobiology of visceral neural afferents and pain sensitivity control [200]. There is evidence that the endogenous analgesia system is abnormal in IBS patients and it is strongly suspected that levels of substance P, cholecystokinin (CCK), NPY, and peptide YY may be related to the pathophysiology of IBS [200].

Patients with IBS often complain of abdominal pain and appear to have a lower sensory threshold to rectal distension. Recognising the potential application of electrical therapy in gastrointestinal conditions, Xiao et al [201] evaluated the rectal sensory thresholds in patients with IBS and to assess whether or not these measurements were affected by the administration of short- or long-term acupoint TENS. Their initial data confirmed that patients with IBS-D have a significantly lower rectal sensory threshold compared to patients with IBS-C or healthy age-matched controls. Following administration of short- and long-term TENS there was a significant elevation of rectal sensory thresholds in the participants with IBS-D,

with patients also reporting a decrease in stool frequency and a decrease in abdominal pain.

At present the authors are unable to explain their findings, however they hypothesise that there could be a TENS-mediated release of the endogenous opioid peptides endorphin and enkephalin. This remains unsubstantiated.

2.10 IFT and treatment-resistant constipation

Interferential stimulation has been used for some time in the treatment of bladder instability due to detrusor overactivity. It was noted that patients undergoing treatment for detrusor overactivity reported a high incidence of diarrhoea following commencement of IFT. This diarrhoea is believed to be as a result of increased colonic transit due to incidental electrical stimulation of the bowel. Consequently, researchers have posed the question as to whether or not IFT could be used as a treatment modality for patients with constipation.

Chase *et al* [170] initiated a pilot study in 2005 that looked at a group of children with treatment-resistant slow transit constipation. Children had had chronic constipation and soiling for a minimum of four years and had had exhaustive medical and behavioural treatment to no effect (n=8). The study found that following a treatment period of only one month there was a significant decrease in the reported incidence of soiling and a significant increase in the incidence of spontaneous defecation. A subgroup of the children had previously had appendicostomies formed in order to be able to perform formal bowel washouts (n=3). This group of children reported a

significantly decreased need for bowel washouts following treatment with IFT, and 2 children were able to stop using their appendicostomy altogether.

2.11 Sacral Nerve Stimulation and Faecal Incontinence

The prevalence of faecal incontinence is estimated to be 3.5% of women and 2.3% of men [202] however it is thought that the actual incidence is likely to be higher due to the stigmata associated with a such a diagnosis. Treatment strategies combine dietary, pharmacology, physiotherapy and surgery in an attempt to minimise symptoms and maximise quality of life. It is only since the 1990s that sacral nerve stimulation has been recognised as an excellent treatment option in the management of this often socially debilitating condition [203].

SNS has been shown to be able to improve faecal incontinence due to physiological *levator ani* and external anal sphincter dysfunction [203] where patients have morphologically intact anatomy. However SNS has also been shown to be of benefit to patients with neuropathic faecal incontinence, cauda equina syndrome [204] and internal anal sphincter dysfunction [203] and even patients with limited structural defects of their internal and external anal sphincters [205]. The ability of SNS to improve faecal incontinence due to such a diverse range of conditions only serves to highlight how little is understood about its possible mechanism of action.

2.12 Summary

Despite many trials supporting the potential use of electrotherapy in the management of a wide range of conditions, its routine use has remained limited to a few areas.

Although TENS is generally accepted by pain specialists as an alternative analgesic tool in the management of several chronic pain conditions, it has failed to attain recognition as a prospective treatment modality by other specialities. Several trials have suggested encouraging results regarding the application of electrotherapy in the management of achalasia, gastroparesis, IBS, constipation and chronic abdominal pain however it has never been incorporated into any of their routine management strategies.

One of the biggest problems regarding the acceptance of electrical therapy is the overwhelming lack of data concerning its precise mechanism(s) of action. Although there are many theories as to the potential effects of electric stimulation, they remain unsubstantiated and thus lack popular support. Many sceptics go so far as to say that any perceived benefits from recipients of electrotherapy are purely due to a placebo effect. Trials have attempted to eliminate this argument by blinding participants with either low-current sham stimulation or by short-circuiting half of the trial machines so that they do not deliver any current despite the dials/displays/lights functioning normally. However, both of these methods have obvious limitations. Firstly, since we are unaware of how electrotherapy works, we cannot be completely sure that even a low level of current may have some therapeutic action. Secondly, electrotherapy tends to result in some sort of sensory stimulation under the electrodes; this is evidently absent when a machine has been short-circuited. As a result it can be argued as to whether or not participants are truly blinded to their treatment pathway. Despite this most studies have shown that improvements from electrostimulation appear to be sustained over a period of time following cessation of

treatment. This is contrary to what would be expected were the effects due purely to a placebo response.

Given that we are unable to explain the effects of different types of electrical stimulation, it may well be that we are currently not utilising the optimal type of electrotherapy for certain conditions. Similarly, at present, we cannot be certain as to the best site of electrode placement, the ideal level of stimulation nor indeed the optimal duration of treatment. If electrotherapy is to become a widely accepted treatment tool, it is essential that these parameters be defined.

Unfortunately, for as long as we are unable to delineate the exact properties and optimal delivery of electrical stimulation we will continue be limited in its application. Until that time, despite having been in use for centuries, electrotherapy is destined to be regarded by most as an "alternative" treatment.

3. Quality of Life

3. Quality of Life

3.1 Definition and general considerations

Quality of life (QoL) can be defined as *"an individual's subjective perception of overall wellbeing and satisfaction with life"* [206] or *"physical, social and emotional aspects of a patient's well-being that are important to the individual"* [207]. QoL is a multidimensional concept that incorporates the assessment of recognised core domains and indicators. It is now widely accepted that in children with chronic disease, traditional medical indicators of outcome are no longer adequate and a comprehensive assessment of health status, or health-related QoL (HR-QoL) is also required [208]. HR-QoL can be further defined as *"QoL measures that are likely to be influenced by health interventions"* [207].

Although HR-QoL measures have been applied in adult populations for sometime, it is only since the early 1990's that such tools have been available for use in children. Most pre-existing adult HR-QoL measures were found to be inappropriate for use in a paediatric population due to either a lack of content validity or an inability to accurately ascertain measurements. Although in some instances adjustments could be made to ensure that the questions conformed to paediatric standards, for the most part there has been the need for the development of original, specific paediatric HR-QoL measures.

3.2 QoL domains and indicators

The term "QoL domains" refers to *"the set of factors composing personal well-being"* and should be regarded as "*the set of elements to which a variable is limited,*

or the range over which the concept of QoL extends" [209]. It is generally accepted that there are 8 core domains: interpersonal relations, social inclusion, personal development, physical well-being, self-determination, material well-being, emotional well-being and rights. QoL domains can be further categorised into "QoL indicators" which are thought of as *"QoL domain-specific perceptions, behaviours, or conditions that give an indication of a person's well-being"* [209] (Table 11). QoL indicators should be (i) functionally related to the respective QoL domain; (ii) able to measure what is intended (validity); (iii) consistent across people or raters (reliability); (iv) able to measure change (sensitivity); (v) able to reflect changes only in the situation concerned (specificity); (vi) affordable; (vii) timely; (viii) person-referenced; (ix) able to be evaluated longitudinally; and (x) culturally sensitive.

Table 11 - *Indicators and descriptors of the core quality of life domains* [209]

Core QoL Domain	Indicators and Descriptors
Emotional well-being	Contentment (satisfaction, moods, enjoyment) Self-concept (identity, self-worth, self-esteem) Lack of stress (predictability, control)
Interpersonal relations	Interactions (social networks, social contacts) Relationships (family, friends, peers) Supports (emotional, physical, financial, feedback)
Material well-being	Financial status (income, benefits) Employment (work status, work environment) Housing (type of residence, ownership)
Personal development	Education (achievements, status) Personal competence (cognitive, social, practical) Performance (success, achievement, productivity)
Physical well-being	Health (functioning, symptoms, fitness, nutrition) Activities of daily living (self-care skills, mobility) Leisure (recreation, hobbies)
Self-determination	Autonomy/personal control (independence) Goals and personal values (desires, expectations) Choices (opportunities, options, preferences)

Social inclusion	Community integration and participation Community roles (contributor, volunteer) Social supports (support network, services)
Rights	Human (respect, dignity, equality) Legal (citizenship, access, due process)

3.3 Types of instruments for measuring QoL

QoL measures are generally used for 3 purposes: (i) discriminative; (ii) evaluative; or (iii) predictive [207]. Discriminative measures are those that determine differences within populations whilst evaluative measures examine changes within an individual over time and predicative measurements are used for prognostication. Additionally, QoL tools can be defined as being either generic or disease-specific [207 208]. Generic instruments have the advantage that they can be used to compare different conditions or patient populations whereas disease-specific instruments have the ability to detect smaller changes in patients with a particular condition. Generic measures can be further classified according to the type of score that they produce (i) health profiles; or (ii) preference-based index measures [207 208]. The former consists of multiple items that are under different *domains* and can be used to assess almost any population. They allow for the quantification of the impact of a disease/treatment on different aspects of a subject's QoL by providing a separate score for each domain. In contrast, the latter provides a single number (or index) that reflects the net aggregate impact of the given situation on all areas of QoL. Preference scores have the advantage that they can be used as an adjustment factor in the calculation of quality-adjusted life years for cost-effectiveness analyses [207 208].

3.4 QoL assessment administration

There is a wide range of variety concerning the administration of QoL instruments with regards to assessor, timing, place and subject. Questions can either be administrated by a trained interviewer or self-administered by the patient. Additionally, questioning can either take place in person, over the phone or via a written survey. If tools require self-completed written responses then they can either be completed in a clinic setting or mailed to the relevant recipients. Each method of delivery and collection has its advantages [210].

It is generally accepted that although the administration of a QoL tool by a trained professional requires more resources, there are consistently fewer errors and missing responses [207]. Conversely, although self-completed instruments are much less expensive to administer, they typically result in missing responses and lower response rates [210]. One answer is to use a supervised self-administered tool that eliminates poor response rates and allows for the immediate addition of any missing data.

Increasingly computers are being utilised both in conjunction with telephone and self-assessment tools to provide a more efficient and accurate means of data collection [210].

3.5 Psychometric properties

Psychometrics refers to the *"measurement of psychological constructs"* [207]. It involves two major aspects: (i) the construction of instruments and procedures for

measurement; and (ii) the development and refinement of theoretical approaches to measurement [210]. The psychometric properties of any QoL tool are essential when deciding whether or not it is an aqequate assessment for clinical or research purposes. When assessing any QoL instrument it is important to consider its *reliability* and *validity*.

Reliability can be defined as *"the proportion of variance that is attributable to the true score of the latent variable"* and is directly responsible for the quality of any measurement. Reliability can be considered in terms of internal consistency and test-re-testing. Internal consistency assesses the agreement of items in multiple-item scales within the same administration whereas test-re-testing replicates measures over time. Internal consistency is defined in terms of Cronbach's α, with a value of > 0.7 being considered acceptable [210].

In terms of QoL tools, validity can be divided into *content validity*, *criterion validity* and *construct validity* [210]. Content validity is *"the extent to which a specific set of items reflects a content domain"* and asks whether or not an instrument samples all of the relevant or important domains. Criterion validity is *"the correlation of a scale with some other measure of the trait or disorder under study"* and ideally compares the tool under question with a 'gold standard' that has already been widely used and accepted. Criterion validity can be further divided into *predictive* validity (the ability to predict something it should theoretically be able to predict) and *concurrent* validity (ability to distinguish between groups that it should theoretically be able to distinguish between). Lastly, construct validity is *"the theoretical relationship of a*

variable to other variables" and refers to the comparison of the new QoL instrument with existing measures [210]. This can also be divided into *convergent* validity (looking at the degree to which the tool is similar to other tools that it theoretically should be similar to) and *divergent* validity (the degree to which the tool is not similar to other tools that it theoretically should be not be similar to).

3.6 Specific paediatric considerations

In most situations it is inappropriate to apply adult HR-QoL tools to paediatric populations since they differ substantially in their activities of daily living and experiences [207 211 212]. Adult tools tend to be too long for children, contain inappropriate language and necessitate sensitivity judgements beyond a child's capacity. Even within the paediatric population it is important to recognise different age groups as separate subsets as they often require the inclusion of different domains or may even need different types (i.e. words vs. pictures) of instruments [210]. When using written tools it is essential that the reading and comprehension levels required to complete the instrument are appropriate for the target population. 10-20% of children can be expected to have learning problems and these problems are likely to be higher in populations of children who have chronic illness or disability [213]. There is a risk that although some children may lack the comprehension required to complete an assessment, they may answer randomly in order to please the examiner [212].

A range of different rating scales are routinely used in paediatric QoL assessment tools including Likert (bipolar scaling method, measuring either positive or negative

response to a statement), facial expression, graphic (i.e. graduated circle size) and visual analogue scales (VAS) [212]. A study assessing the relationship between the type of scale used, the age of the subject and consequent reliability concluded that for maximum internal reliability, graduated circles should be used for ability items whilst faces were recommended for social items. In terms of maximum reproducibility over time, a VAS is suggested for use in children aged 5 to 6 and faces for children aged 7-9 years [212].

3.7 Use of proxy vs. self-assessment for paediatric QoL evaluation

Until relatively recently, evaluation of a paediatric subject's QoL has relied purely upon proxy assessment, with children being deemed too unreliable to be able to accurately quantify their situation [213]. It was often assumed that young children are unable to distinguish between fantasy and reality, however more recent studies suggest that this is simply due to their limited experience and not a lack of their ability. This limited experience can also mean that children are unable to appreciate that life is different for others and adds a further challenge in the development of reliable assessment tools. It is now generally accepted that although children may interpret events differently from their adult counterparts, given the correct circumstances, they are perfectly capable of remembering, reporting and applying information [213].

Research has shown that children's understanding of self develops sequentially, relative to their cognitive and language development [214]. A major change in a child's sense of self occurs between the age of 18 months and 2 years of age, where they

begin to develop cognitive representations of themselves and the ability to distinguish between self and others [215]. Whilst children below the age of 6 tend to see themselves in physical terms and have difficulty separating their sense of self from their actual behaviour, it is strongly believed that they have the ability to describe their mental state and appreciate that feelings are different from actions [216]. Children at this age have a basic understanding of health focussed around hurts, aches and eating the right foods [217]. As children approach middle childhood (6-12 years) they begin to develop an increasing awareness of their self and a growing appreciation of their emotions and their understanding of health and illness increase alongside their perception of bodily functions (a differentiated biological model) [218].

3.8 Reliability of proxy assessment

A proxy's perception of a subject's QoL may not represent an accurate description of their actual thoughts and feelings. There are mixed opinions as to the reliability of proxy assessments [219]. It appears that the correlation between parent and child perception of QoL differs substantially according to domain [207 212 213 219]. In children with chronic illness, good agreement is generally reported for physical activities (functional status), physical symptoms and somatic distress [219]. Conversely, there appears to be moderate to poor correlation within domains that reflect more social or emotional QoL issues [219]. There is also mixed evidence with regards to the reporting of the overall level of QoL between children and their parents. Although some studies suggest that there is no significant difference in global perception, there are many that propose that parents consistently report a significantly lower QoL than their child [219].

There is good reported correlation between a doctor's and a parent's assessment of a child's QoL [220], however it appears to be poorer between nurses, parents and children [221]. However, although there are studies assessing the difference between medical staff and parents as proxy raters, there are no studies that address the potential discrepancy between maternal- and paternal-reported QoL [219].

There have been various studies that have looked at the impact of age, gender and illness on parent-child agreement. One study reports that for children (8-12) there is maximum correlation for cognitive functioning, however for adolescents the agreement was greatest for physical functioning [222]. There have been no clear findings with regards to the influence of gender upon concordance of parent-child reporting [223]. When considering disease state, there appears to be a wide variation in correlation between illnesses [224 225] and also between states of wellness, temporary illness and chronic illness [223 224].

There is no surprise that there appears to be greater parent-child agreement for questionnaires completed at home compared to those completed in a clinical setting [226]. This highlights the importance of consideration and documentation of setting when administering QoL tools.

3.9 The use of QoL measures in clinical trials

QoL is a central issue when considering the impact of chronic disease and so should not be ignored by researchers [227 228]. With the advent of improved treatment and

resultant prognosis for many chronic illnesses, there is the reality that more children are faced with living with long-term ill-health and the effect on their resultant standard of life must not be forgotten. Although traditionally research has focused on objective indices including survival rates and reduction in physical symptoms, investigators are now tending towards the routine inclusion of HR-QoL tools. Indeed for many families, an improvement in their child's QoL is far more important than any change in their clinical state. As previously described it is important to consider whether or not a tool adequately assesses a trial population's disease, what its psychometric properties are, how long is it and who needs to complete it [210].

Specific concerns when using QoL instruments in clinical trials include *economics*, *maturation* and *response shift* [228].

3.10 Economics

It is the concern of some researchers that adding QoL measures to a trial protocol may increase the monetary cost of the study. In addition, there are also concerns about the cost in time associated with the attainment of meaningful data. However, it is becoming increasingly evident that the omission of such tools reduces the value of many projects and that their inclusion is entirely justified. It is important to remember in the context of multicentre trials that a tool must be suitable for use in all recruited centres. The more data that can be collected, the greater the statistical power will be [210].

3.11 Maturation

Maturation should be considered in terms of both short- and long-term issues. In the short-term, if QoL tools are administered too frequently it can result in fatigue and learning [228]. Equally, in the long-term, psychophysical development and both cultural and environmental changes can affect responses [229]. In order to minimise these effects it is important to try to utilise a versatile measure and administer it as sensitively as possible [229].

3.12 Response shift

Three types of response shift can be identified: (i) recalibration of scales comprising the yardsticks respondents use to gauge personal standards; (ii) actual changes in values as measured by ranking of outcome domains; and (iii) redefinition of the target construct [230]. Response shift was first identified when it became obvious that there were frequent discrepancies between clinical features of a disease and patients' self-reports about their quality of life. Over time patients adjust to their condition and its associated difficulties and may meet with others who are faced even more restrictions then they are. With this in mind, it is important to recognise and report any response shift and to assess its subsequent impact on ratings [230].

One way of recognising any response shift is by using "then" ratings [229]. This method employs the use of pre-, post-testing with the addition of a "then-test" when the post-test is completed. The "then-test" represents a retrospective pre-test. By comparing the post- and then-tests, treatment-induced response shift effects can be eliminated, allowing the detection of unconfounded treatment effects. In addition, by

comparing the pre- and then-tests, an estimate of the amount and direction of the response shift can be made [229].

3.13 Specific QoL tools for faecal incontinence/constipation

There exist several HR-QoL tools that have been developed specifically for the assessment of patients with defecatory disorders. Their use is primarily targeted towards an adult population as many include sexual activity, work functioning and length of symptoms (up to > 20 years). The number of tools that are available for the assessment of faecal incontinence highlights the lack of uniform acceptance of any one model.

There are 3 types of disease specific measures: (i) a traditional condition-specific QoL instrument; (ii) a "systemic" QoL tool that assesses the system (i.e. gastrointestinal, respiratory, cardiac) that the condition affects; and (iii) a population-specific condition-specific QoL tool that assesses QoL relative to a specific population (i.e. incontinence in children with Hirchsprungs disease, incontinence after anorectal malformation repair).

3.14 Traditional condition-specific QoL tools

3.14.1 Fecal Incontinence Questionnaire

This represents a self-reported questionnaire designed to measure the prevalence of faecal incontinence in a community and the risk factors associated with incontinence (Appendix 1) [231]. It has specific questions designed to: (i) assess general bowel habits and symptoms; (ii) determine the presence of faecal incontinence and in those

with an affirmative response, characterise and measure the severity; (iii) measure associated symptoms related to pelvic floor dysfunction; (iv) assess historic risk factors that may contribute to the development of faecal incontinence; and (v) help assess the association between urinary symptoms and faecal incontinence. The questionnaire has been tested by the authors for feasibility, test administration, reproducibility, validity and reliability and they report mixed but generally acceptable results [231]. There does not seem to be a scoring method associated with the tool meaning that it is not suitable for measuring change. It has not been used in children [231].

3.14.2 Fecal Incontinence Quality of Life Scale (FIQL)

This QoL instrument is composed of a total of 29 items forming 4 scales: (i) Lifestyle (10 items); (ii) Coping/Behaviour (9 items); (iii) Depression/Self-Perception (7 items); and (iv) Embarrassment (3 items) (Appendix 2) [232]. The responses for all items are scored by a five-point Likert scale). The FIQL has been psychometrically evaluated for reliability (test-retest and internal consistency) and validity with acceptable results and each of the 4 scales is reported to be capable of discriminating between patients with faecal incontinence and other gastrointestinal disorders. It has been endorsed by the American Society of Colon and Rectal Surgeons (ASCRS) [233]. The FIQL is not directly applicable to children as it contains items with sexual references.

3.14.3 Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL)

The PAC-QOL was designed to complement the PAC-SYM (patient assessment of constipation symptoms) and was designed to address the need for a standardised, patient–reported outcome measure to evaluate constipation over time [234] (Appendix 3). The tool consists of 28 items that form 4 subscales: (i) worries and concerns; (ii) physical discomfort; (iii) psychosocial discomfort; and (iv) satisfaction. The scores are combined to give an overall scale. Multicentre/multinational testing revealed acceptable results for both internal consistency reliability (Cronbach's $\alpha > 0.80$) and reproducibility (Test-retest intra-class correlation (ICC)> 0.70). The PAC-QOL was also shown to be responsive to improvements over time. All of the psychometric testing has involved an adult population and there is no reported evidence of either tool being used with children [234].

3.15 "Systemic" QoL tools

3.15.1 Gastrointestinal Quality of Life Index (GIQLI)

This is a bilingual (English and German) questionnaire containing 36 items each with 5 response categories (Appendix 4) [235]. The responses to the questions (0-4) are summed giving a numerical score (0-144). The GIQLI consists of a set of core questions that are applicable to any patient with any gastrointestinal disease. It is designed to provide a subjective perception of well-being and is not intended to be used as a diagnostic tool. The questionnaire has been tested for reliability, validity and internal consistency (in German) and the authors report levels that are well above accepted standards (Cronbach's $\alpha > 0.90$, ICC 0.92). They also claim that the index

is responsive to changes in the clinical status of patients. There have been no reported results for testing of the English version and it has not been validated in children.

3.16 Population-specific, disease-specific QoL tools

3.16.1 Modified Manchester Health Questionnaire (MMHQ)

This QoL tool (Appendix 5) represents a combination of the Faecal Incontinence Severity Index [236] (FISI) and the Manchester Health Questionnaire (MHQ) [237]. It has been designed, and validated, for telephone administration in an attempt to provide a measure for use in clinical trials that is cost-effective. It has satisfactory reported reliability and validity standards (Cronbach's α = 0.79-0.92, ICC = 0.75) for written and telephone administration. The responsiveness of the MMHQ to changes in clinical status is yet to be determined in a longitudinal study. Although it was initially formulated to assess faecal incontinence in females after vaginal delivery, by the omission of 1 section it is appropriate for use in all adults. It is not suitable for use in children.

3.16.2 Ditesheim and Templeton QoL scoring system

This represents a simple quantitative five-item QoL tool evaluating the three domains of personal development (school attendance), social inclusion (social relations) and physical well-being (physical capabilities) (Appendix 6) [238]. It was initially developed as a tool to assist in the assessment of short-time vs. long-term QoL in children following repair of high imperforate anus. It includes questions about school attendance, social difficulties and physical capabilities. Where questions are

age specific, if irrelevant, the items are omitted and the score then modified accordingly.

Unfortunately there is little information available regarding the psychometric properties of this scoring tool [233] and hence it's ability to accurately assess QoL is questionable. Even if all questions are answered, the small scoring range (0-3.5) produces low precision and affects the tool's ability to detect differences. Although the content of the questions are valuable, there are too few questions for this measure to truly be able to reflect disease specific QoL. It is however one of the few tools designed to assess faecal incontinence that is intended for use in children.

3.16.3 Patient Assessment of Constipation Symptoms (PAC-SYM)

The PAC-SYM is a 12 item self-reported tool that is divided into 3 domains (i) abdominal; (ii) rectal; and (iii) stool [239 240] (Appendix 7). It was initially devised in an attempt to address the obvious lack of a gold standard for assessment of HR-QoL of patients with constipation. It is specifically designed to measure symptoms and their severity and is intended to be used in conjunction with PAC-QOL (Patient Assessment of Constipation Quality of Life) which is itself is designed to assess QoL. The authors of the PAC-SYM instrument report high internal consistency and test-retest reliability (Cronbach's $\alpha = 0.89$, ICC = 0.75) and they feel it is a valuable tool for evaluation of chronic constipation. They do however highlight that testing in multiple clinical settings suggested that additional clinical data were necessary to perform a complete assessment.

3.16.4 Quality of Life Score for Children with Fecal Incontinence

A group of researchers following up a cohort of children after surgically corrected anorectal malformation identified that there was no QoL scale in existence and so formulated their own tool [241]. Their instrument consists of 6 items based on somatic, social and psychological domains and is parent-reported (Appendix 8). The authors feel that although they have not performed any official reliability or validity testing, the tool is sensitive enough to reflect changes in QoL. They acknowledge that further psychometric testing is necessary.

3.16.5 Defecation disorder list (DDL)

This represents a disease specific HRQoL tool for children with constipation or functional non-retentive faecal soiling [242]. It is only relevant for usage in children who experience soiling as a consequence of their constipation. It consists of 37 items in 4 domains - constipation related, emotional functioning, social functioning and treatment/intervention. Its reliability and reproducibility were assessed based upon its use in only 27 children. The authors describe good reliability for all domains with Cronbach's α ranging between 0.61 and 0.76. ICCs for all 4 domains ranged between 0.82 to 0.92. When validity based on comparison to the TACQOL tool was assessed, the authors reported only moderate results.

3.17 Paediatric generic QoL tools

Generic QoL instruments present several advantages when assessing QoL within a disease-specific population. Most importantly they allow the comparison of the target population with other populations in whom a disease specific QoL tool would

be irrelevant. By using a generic tool, subjects with constipation/faecal incontinence can be compared with subjects with other chronic disease states as well as healthy control subjects. Unfortunately generic tools often lack the subtle qualities, or *responsiveness*, required to detect "change". Responsiveness is viewed in the context of 2 central questions: (i) how much change is meaningful (in a particular area, such as clinical or personal change)?; and (ii) how much change must occur before the instrument is capable of assessing the change? [243]. Generic tools are usually capable of detecting gross changes but are often poor at picking up small variations.

There exists no gold standard for the assessment of a child's QoL [218]. Instead, several tools are available, providing a combination of self- and proxy-reported instruments.

3.17.1 The Child Health Questionnaire (CHQ, CHQ-PF50, CHQ-PF28)

Originating from the United States of America (USA) the CHQ represents a self-report instrument for children aged 10-18 years [244] designed to assess "physical and psychosocial functioning and well-being". It consists of 87 items addressing 14 different concepts of physical and psychosocial health and associated impairments (physical ability to function, bodily pain, general health perception, self-esteem, mental health, behaviour, burden on parents, social impairment and family activities). Scores can be aggregated into physiological and psychosocial sum values. In addition, in response to industry demands for instruments of a more practical length, a 50-item (CHQ-PF50) and a 28-item (CHQ-PF28) parent-

completed were created. The authors report mixed reliability with Cronbach's α ranging from 0.62-0.91 across the instruments [244].

More recently the SF-10 (short form -10) has been developed (based on the CHQ range of instruments) which is a parent-completed QoL assessment tool for children, aged 5-18 years, consisting of just 10 questions. It addresses eight domains of health (physical functioning, role limitations due to physical health (role-physical), bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems (role-emotional) and mental health) and, like its CHQ counterparts, is scored to produce physical and psychosocial health summary scores.

3.17.2 The Child Health and Illness Profile (CHIP)

Again developed in the USA, this tool is designed primarily to assess functional aspects of HR-QoL in adolescents aged 11-17 years [245 246]. It is divided into 6 broad domains (satisfaction, complaints, resilience, health conditions, attainment of social goals and risk behaviours) which are further subdivided into 20 smaller domains. The scoring system is designed to produce taxonomy of health profiles owing to its high psychometric quality. Although the authors report good reliability (Cronbach's α exceeds 0.7 for all domains), the sample on which the questionnaire was standardised is not felt to be representative of the 'general population', nor were large numbers assessed [247]. Consisting of 188 items, the instrument is somewhat lengthy for a paediatric self-assessment tool and the majority of its content was not designed with input from children and adolescents.

3.17.3 The How Are You Questionnaire (HAY)

Originating from the Netherlands, HAY assesses generic and disease-specific aspects of QoL and is designed for children aged 7-13 years [247]. It can either be self- or proxy-completed. It contains questions from 6 generic domains (physical activities, cognitive tasks, social activities, social problems, physical complaints and treatments) as well as 2 chronic illness (concerns and feelings of inferiority) and 2 disease-specific (physical complaints and treatment tasks) domains. Unfortunately, it is rather lengthy (80 items) and although it is advertised as a generic tool, its inclusion of chronic illness/disease-specific domains limits its use in healthy control subjects.

3.17.4 The KIDSCREEN Quality of Life Questionnaire

The KIDSCREEN-52 is a generic questionnaire for children aged between 8 and 18 years of age that was developed simultaneously in 12 European countries [248] [249]. Questionnaire development included focus group discussions with children and adolescents and the result was a 52-item, 10 domain self- or proxy-assessed QoL instrument. Since its initial creation the KIDSCREEN has been modified, and there now exist 2 short forms: the KIDSCREEN-27 (27 items, 5 domains) [250] and the KIDSCREEN-10 (10 items, 1 domain) [251]. This QoL tool is the first of its kind to comprehensively fulfil the standards promoted by the World Health Organisation (WHO) for a child-suitable measurement of HR-QoL [247]. As yet, although its authors report encouraging psychometric testing results (Cronbach's α 0.77-0.89), it is not widely available for use and all data relate solely to pilot testing.

3.17.5 The KINDL Questionnaire for Measuring HR-QOL in Children and Adolescents

The KINDL QoL measure originates from Germany but has now been translated into 14 languages [252]. There are 3 versions that are age appropriate: KINDL-Kiddo (13-16 years), KINDL-Kid (8-12 years) and KINDL-Kiddy (4-7 years). All measures come in both self- and parent-reported forms. The KINDL questionnaire is developed from a conceptual model that includes 4 main components of QoL: psychological well-being, social relationships, physical functions and everyday-life activities and consists of 24 items divided into 6 domains (physical health, general health, family functioning, self-esteem, social functioning and school functioning). Although the authors have demonstrated good internal consistency (Cronbach's $\alpha >$ 0.75) and test-re-test reliability (ICC = 0.8), current data suggest that the tool is unable to show a significant difference between healthy and ill children.

3.17.6 TACQOL (The Netherlands Organisation for Applied Scientific Research-Academic Medical Centre Child QoL Questionnaire)

This tool was developed in the Netherlands for use as a generic instrument in medical research and clinical trials [253]. It consists of 56 items that are divided into 7 domains (physical complaints, mobility, independence, cognitive function, social function, positive emotions and negative emotions) each with 8 questions. There are 2 versions; a self-reported tool for children aged 8-15 years (Cronbach's α 0.59-0.86) and a proxy-reported tool for children aged 5-15 years (Cronbach's α 0.71-0.89). The questions are designed so that the quantity of any impairment can be assessed and then the subsequent emotion to this impairment evaluated. Although it is a well-

designed tool for quantifying QoL in children with illness, the questions were not originally designed for use in healthy subjects.

3.17.7 Pediatric Quality of Life Questionnaire (PedsQL)

The PedsQL range of QoL tools includes several generic and disease-specific questionnaires [222 254-260]. The instruments were developed to assess QoL in paediatric subjects from 2 to 18 years and exist in self- and parent-report forms that are designed to be used in parallel, providing a direct comparison between child- and parent-perceived QoL. The PedsQL 4.0 Generic Core Scales version (Appendix 9) consists of 23 items from 4 domains (physical, emotional, social and school). The answers to the questions can be computed to give separate physical and psychosocial summative scores as well as an overall assessment of QoL. Cronbach's α is reported as 0.93 for both the child-report and parent-report tools. PedsQL is a short but reliable tool that is suitable for use in clinical trials, research, clinical practice, school health settings and community populations [247 261].

3.17.8 Summary of use of reviewed Quality of Life tools in adults and children with defecatory disorders and slow transit constipation

Table 12 - *Table summarising the use of Quality of Life tools in adults and children with defecatory disorders and slow transit constipation.*

Name of QoL Tool	Validated in adults/children	Reported use in adults/children with defecatory disorders	Reported use in subjects with STC
Fecal Incontinence Questionnaire	Adults [231]	Adults	No
Fecal Quality of Life Scale	Adults [232]	Adults [233]	No
Patient Assessment of Quality of Life Questionnaire	Adults [234]	Adults [262]	No
Gastrointestinal Quality of Life Index	Adults [235]	Adults [263 264] and children [265]	Adults [266-269]
Modified Manchester Health Questionnaire	Adults [237]	Adults [270]	No
Ditesheim and Templeton	Children [238]	Children [271]	No
Patient Assessment of Constipation Symptoms	Adults [240]	Adults [262]	No
Quality of Life Score for Children with Fecal Incontinence	Non-validated	Children [241]	No
Defecation disorder list	Children [242]	Children [272]	No
Child Health Questionnaire	Children [244]	Children [273]	No
Child Health and Illness Profile	Children [274]	No	No
The How Are You Questionnaire	Children[247]	No	No
KIDSCREEN Quality of Life Questionnaire	Children [249-251]	No	No
The KINDL Questionnaire for measuring HR-QOL in Children and Adolescents	Children [252]	No	No
TACQOL	Children [253]	Children [275 276]	No
Pediatric Quality of Life Questionnaire	Children [255 256]	Children [277]	No

3.18 Summary

Quality of life is now recognised as an important clinical measure that should form part of routine clinical assessment and follow-up in order to fully evaluate the

efficacy of any intervention. As such, many generic, population-specific and disease-specific QoL tools now exist and QoL assessment has almost become standard practice in adult medicine.

As culture has changed, accepting that children should no longer be 'seen and not heard', but be allowed to voice their opinions, so trends in paediatric QoL assessment have changed recognising that parental proxy-assessment should ideally be complemented by child self-assessment where possible. The PedsQL QoL series of questionnaires consist of parallel child and parent assessment tools and provide a valuable insight into differences in QoL perception.

Unfortunately, as yet, there exists no condition-specific, population-specific tool for children with chronic constipation. Tools are in existence for adults with faecal incontinence, however, a large part of their questions focus on sexual function and so their application in children is limited. Similarly, there are many generic tools that assess QoL in paediatric populations, but none of them seem to address the specific problems faced by children with intractable constipation. Hopefully, as more studies highlight potentially serious QoL issues in a diversity of populations and conditions, then more tools will become available to intimately evaluate QoL in specific disease states.

4. Hypothesis and aims

4. Hypothesis and Aims

This thesis hypothesises that there exists a form of chronic constipation in children (slow transit constipation (STC)), characterised by abnormal colonic motility, that not only can be reliably diagnosed by nuclear transit studies or colonic manometry, but also can be treated by transcutaneous electrical stimulation.

The first aim of this thesis was to establish whether or not living with the daily stresses of slow transit constipation (STC) adversely affect a child's quality of life (QoL). This was tested by assessing the QoL of populations of both children with QoL and healthy controls. QoL was measured by parallel parent proxy-reported and child self-reported questionnaires. There are no previous studies that have evaluated the QoL in children with STC.

The second aim was to establish the test-re-test reliability of nuclear transit studies in the diagnosis of children with slow transit constipation (STC). This was determined by identifying children with STC who had had transit studies performed on two, separate occasions and comparing the results of the two studies.

Thirdly, this thesis aimed to evaluate the efficacy of a novel form of therapy in the treatment of children with STC. It reports the interim analysis of a randomised placebo-controlled trial assessing the potential application of transcutaneous interferential electrical therapy in the management of children with chronic constipation unresponsive to at least 2 years of conventional treatment.

Finally, the last aim of this thesis was to ascertain whether or not there was any change in the colonic motility pattern of children with STC following treatment with IFT. This was ascertained by performing colonic manometric studies both before and after treatment with IFT and comparing the findings.

In summary, this thesis aimed to assess novel aspects of diagnosis and management in the evaluation and treatment of chronic childhood constipation.

5. Quality of life in children with slow transit constipation [278]

5. Quality of life in children with slow transit constipation

5.1 Introduction

Since its first description in 1996 [19], slow transit constipation (STC) is gradually becoming accepted as a chronic form of constipation in children [20 146 277 279-281]. It is characterised by intractable constipation that is not readily responsive to laxatives, diet or a change in lifestyle and where there is marked delay in colonic transit time on transit study [69 70].

The aetiology of STC remains unknown with various theories involving neuronal abnormalities [74 282], genetic linkage [92 280], endocrine dysfunction [283], autonomic dysfunction [30] and abnormal colonic pacemaking [48] being postulated. Children with STC suffer from irregular bowel motions, colicky abdominal pain and frequent uncontrollable soiling. In some children, despite aggressive medical therapy, spontaneous passage of stools is unachievable. Consequently these children are managed by the surgical formation of an appendicostomy through which regular antegrade bowel washouts can be performed to improve continence [126 128]. Definitive treatment remains elusive and consequently families of children with STC are offered a wide range of management options, many of which are perceived to be unsuccessful.

There are many studies that have assessed the quality of life in children with chronic disease, however few studies exist that look at the physical and psychosocial impact of gastrointestinal disorders in children [238 241 275 276], with only a few concentrating on those with chronic constipation [265 273 277]. Currently no studies exist that have

examined the quality of life in children with STC. The only studies that have evaluated QoL in subjects with STC are those that have compared QoL in adults before and after bowel resection [266-269].

The value of any trial is inextricably linked to the quality of the data that is recorded. Standardisation of recorded outcome measures is being called for as a way to reduce to risk of inappropriate measurements (especially in children), make it easier to compare and contrast trials and to minimise any risk of outcome reporting bias [284]. It is being increasingly recognised that the reporting of QoL should form part of any standard outcome measures in clinical randomised controlled trials (RCT) [285 286].

A review concerning both the frequency and quality of reporting of QoL in RCTs on the Cochrane Controlled Trials Register (CCTR) from 1980-1997 found that less than 5% of all RCTs during this time period described any evaluation of QoL [287]. At the start of the study period, only 0.63% of registered trials reported assessment of QoL measures. However a similar trial that reviewed all RCTs registered on the CCTR from 2002-2008 found the recording of QoL had become a primary outcome measure in 25.4% of trials with 14% of trials using supplementary reports (separate from the first publication) to recount their findings [288]. This increased rate of inclusion of QoL as an outcome measure highlights the importance that is now being placed on its evaluation in clinical trials and further serves to justify the establishment of the reported study.

5.2 Hypothesis and aim

The study hypothesises that the clinical features of STC have an impact upon physical, emotional and social function. This study, using a validated paediatric questionnaire (PedsQL), aimed to assess physical and psychosocial features of life in children with STC and compare it with control subjects.

5.3 Subjects and Methods

5.3.1 Study population

Study patients were recruited from the gastrointestinal and surgical clinics in a large tertiary paediatric hospital (Royal Childrens Hospital, Melbourne, Australia). Patients were between 8 and 18 years of age and had been treated for constipation for a minimum of 2 years. Constipation was defined by the Rome II criteria [289] and all patients had previously had metabolic or hormonal causes excluded. All subjects were diagnosed with STC by radioisotope nuclear transit study and had retention of radioactivity in the proximal colon at 48 hours [69]. Children with an organic cause for their constipation, cognitive impairment or anorectal retention/normal transit on their nuclear transit study were excluded. Control subjects were recruited from: (i) out-patient surgical clinics and consisted of children (8-18 years) who were attending for routine follow-up after uncomplicated appendicectomy or minor surgical procedure (i.e. scrotal exploration, orchidopexy, herniotomy); and (ii) a scout jamboree that took place locally during the recruitment period. All control subjects had a "normal" bowel pattern (between 3 movements a week and 3 movements a day where the stool is brown or golden brown in colour, formed, has a texture similar to peanut butter, and a size and shape similar to a sausage). Children who had concurrent co-

morbidities were excluded along with those who did not describe a "normal" bowel habit.

5.3.2 Methods

Following the attainment of informed consent, the questionnaire (PedsQL) was administered by one of two investigators (MC or CC). The PedsQL 4.0 (Pediatric Quality of Life Inventory) Generic Core Scales consist of parallel child and parent self-report scales, and have been validated in children and adolescents aged 2-18 [254-256 259]. The questionnaires consist of 23 items encompassing (i) Physical functioning (8 items) (ii) Emotional functioning (5 items) (iii) Social functioning (5 items) and (iv) School functioning (5 items). The categories can then be grouped into Physical (i) and Psychosocial (ii, iii & iv) functioning. The questions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilised (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse scored (0 =100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) and linearly transformed to a 0-100 scale by dividing the total score (maximum 2300) by the number of questions (23). Higher scores indicate better quality of life (maximum score = 100).

Parent and child completed the questionnaire independently with impartial assistance being provided for any child who had difficulty with comprehension.

The local human research ethics committee (HREC) approved the study (23040 B).

5.3.3 Outcome measures

The primary outcome measures were self- and parent-reported, health-related quality of life (HR-QoL) in children with STC compared with healthy controls.

5.3.4 Data Analysis

Physical, psychosocial and total quality of life scores were compared using Wilcoxon matched pairs and Mann Whitney tests. All P values < 0.05 were considered as statistically significant.

5.4 Results

From March 2006 to March 2007, 51 children (34 Male, 17 Female) with STC and 79 healthy controls (48 Male, 31 Female) were recruited into the study (Table 13). All children and their parents successfully completed the PedsQL. The data for every group did not have a Gaussian distribution.

The QoL scores (PedsQL) for all the study participants are summarised in Table 14.

Table 13 - *Demographics of study population.*

	STC Patients	Controls
Number	51	79
Male:Female	2:1	1.9:1
Mean Age (years)	11.5	12.1
Mean duration of symptoms (years)	10.1	N/A
Appendicostomy	14/51	N/A
Soiling	41/51	N/A
Abdominal pain	40/51	N/A

Table 14 - *Child and parent QoL scores (PedsQL) for control and STC groups (mean and standard deviation (SD))*

	Total QoL score		Physical QoL score		Psychosocial QoL score	
	Mean	SD	Mean	SD	Mean	SD
Child - control	85.99	9.471	92.14	7.799	83.30	11.15
Child - STC	72.90	16.00	78.79	14.79	69.22	18.32
Parent - control	84.25	8.644	92.77	9.247	79.71	11.10
Parents - STC	64.43	19.57	74.44	20.76	58.55	21.86

Child-reported QoL was significantly lower in children with STC compared to normal children (mean 72.90 vs. 85.99; $p < 0.0001$) (Figure 13). Parent-reported QoL was significantly lower for children with STC compared to the control group (mean 64.43 vs. 84.25; $p < 0.0001$) (Figure 14). Physical and psychosocial QoL, both child- and adult-reported, were consistently poorer in the children with STC (Figures 13 and 14).

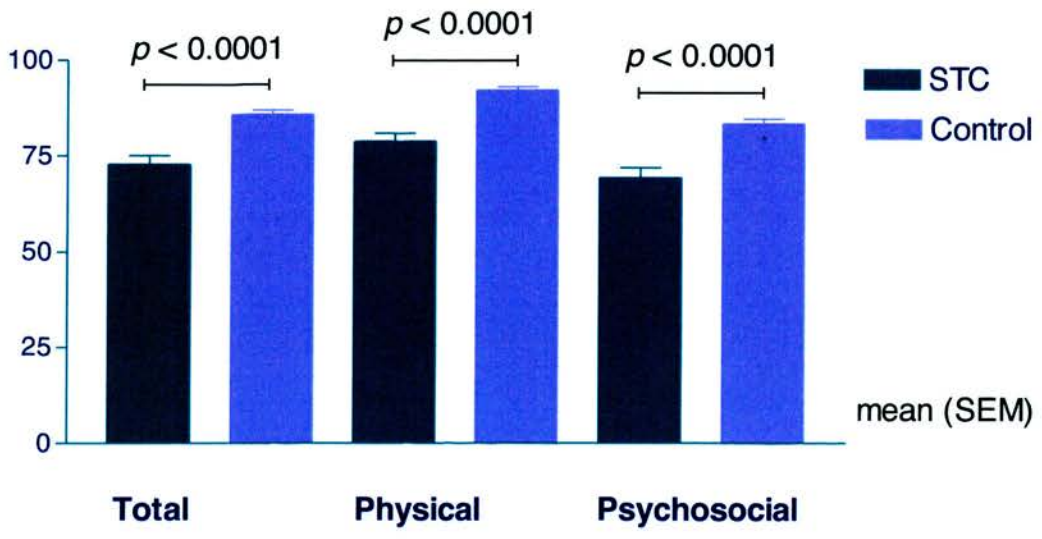

Figure 13 - *Child-reported scores: STC vs. control (Wilcoxon matched pairs test).*

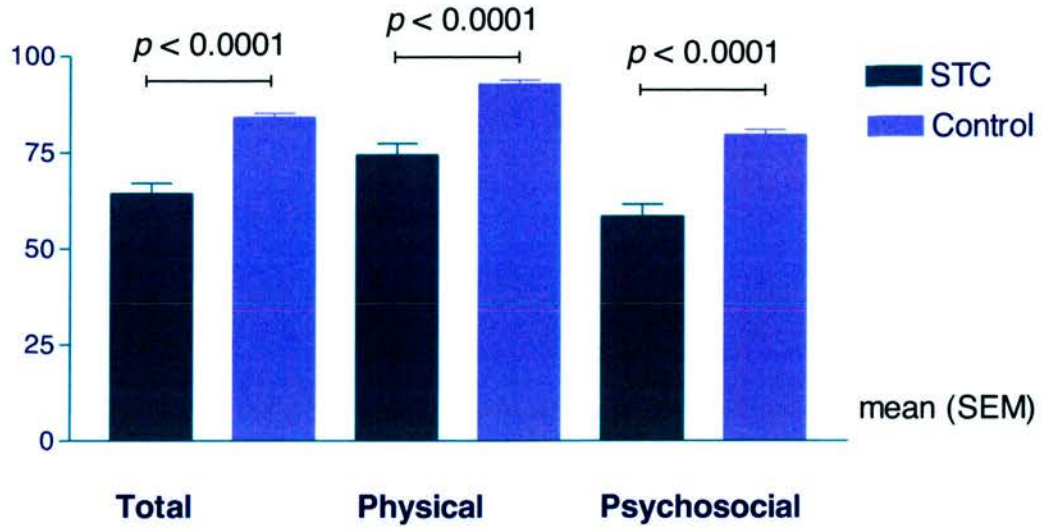

Figure 14 - *Parent-reported scores: STC vs. control (Wilcoxon matched pairs test).*

Parents of children with STC reported their child had a significantly lower QoL than the children themselves reported (64.43 vs. 72.90; $p = 0.014$) (Figure 15). This was also apparent in the control group, however to a lesser extent (84.25 vs. 85.99; $p = 0.04$) (Figure 16). Parents both of children with STC and of controls reported significantly poorer psychosocial QoL for their child compared to the child's own report (Figures 15 and 16). There was no statistical difference in the reporting of physical QoL (Figures 15 and 16).

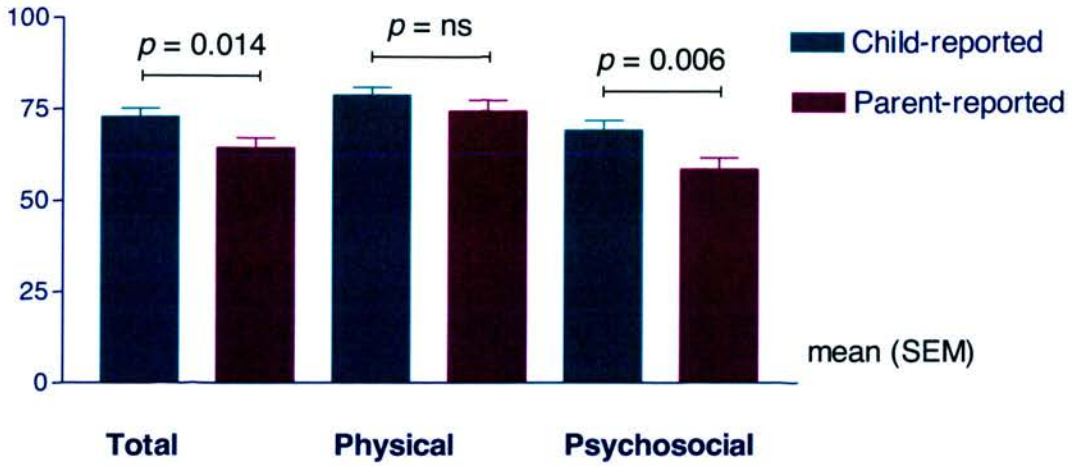

Figure 15 - *STC: Child- vs. Parent-reported scores (Mann Whitney test).*

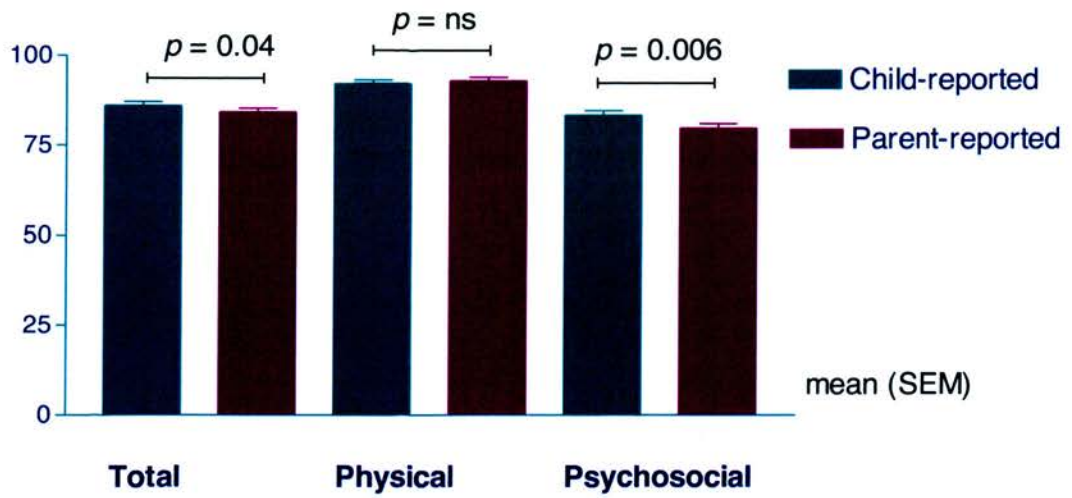

Figure 16 - *Control: Child- vs. Parent-reported scores (Mann Whitney test).*

5.5 Discussion

Quality of life (QoL) can be defined as *"an individual's subjective perception of overall wellbeing and satisfaction with life"* [206] or *"physical, social and emotional*

aspects of a patient's well being that are important to the individual" [207]. QoL is a multidimensional concept that incorporates the assessment of recognised core domains and indicators.

Many studies have looked at the QoL in children with chronic disease, however there are few studies that have specifically examined the impact of chronic constipation on physical and psychosocial functioning [277]. There are no current publications that address QoL issues in children with proven STC. This is a population of children who have in many instances been managed for several years without a definitive diagnosis and often ineffectual treatment, and for whom social interaction is often limited due to antisocial symptoms (i.e. soiling).

This study found that there is a significant impairment in QoL of children with STC compared to healthy controls. This is consistently described by the children and their parents and affects both physical and psychosocial QoL (Figures 13 and 14).

Parents of children with STC often describe the onset of their child's symptoms as being at, or shortly after, birth [20]; STC represents a lifelong problem. These children grow up with the daily problem of difficulty with stooling, chronic abdominal pain and frequent soiling. Their social interactions are often limited due to the lack of insight of their young peers and consequently they can become withdrawn and socially isolated.

Although children with STC have no obvious physical anomalies, both the children themselves and their parents report a significant deficit in their physical QoL. Questions included in the physical section of PedsQL ask about participation in sport, ability to take bath/shower by oneself, having hurts/aches and energy levels. If children experience involuntary passage of stool, or soiling, then participation in sport can often seem daunting. Not only do children have to change in a communal area, where they may inadvertently expose protective clothing or their appendicostomy site [126 127], but they may also experience increased symptoms associated with the increase in physical exertion. Similarly, if children experience severe soiling then they may require assistance to adequately clean themselves. As previously mentioned, children with STC are often affected by chronic abdominal discomfort. This chronic pain can account for the increased reporting of hurts/aches and also the consistent reporting of low energy levels. In addition, children affected by the slow passage of stool often feel full and bloated and complain of a poor appetite. Their resultant decreased calorific intake will also contribute to their low energy levels.

The psychosocial section of PedsQL is divided into emotional, social and school functioning. Emotional functioning covers feeling afraid, sad or angry as well as troubles sleeping and worrying about the future. Feeling strong emotions and worrying about the future are in many ways features of childhood in general and cannot always be attributed to chronic disease. Despite this, the subgroup of children with STC reported significantly poorer emotional QoL and in particular many were concerned about how their future might be affected by their condition.

Social functioning enquires about the ability of the child to integrate with others. Questions focus on ability to get on with other children as well as social acceptability (other children wanting to be their friend/teasing) and ability to keep up with their peers. Children are often admired for their honesty and integrity, however it is well known that they can also be incredibly cruel especially when they lack insight. Children who are afflicted with chronic soiling are unfortunately easy targets for social ridicule and bullying. Although the responses of the children with STC suggest that they feel they have the ability to keep up with their peers, they have poor QoL scores for social functioning due to their reduced social integration.

The final section of psychosocial QoL concerns school functioning. Subjects are asked about their ability to pay attention, memory, keeping up with schoolwork and missing school either because of feeling unwell or because of the need to visit a medical professional. As previously discussed, some of these questions will score similar answers when asked to all children, especially those relating to paying attention and forgetting things. However, the children with STC again score significantly lower on this section due to poorer school attendance and frequent medical needs.

This study also showed that although children with STC and their parents both describe a significantly poorer QoL than healthy children, the parents report a lower QoL than their own children (Figures 15 and 16). There are several reasons why the parents may report a poorer QoL. Parents have an objective ability to look at their children compared to their peers and become distressed by any apparent differences.

Since children with STC often have a family history of constipation, their parents may have had similar experiences at school, thus affecting their scoring. As previously mentioned, STC usually represents a lifelong condition. Children who suffer with STC grow up with their condition and the lifestyle that it entails and have no other experiences to which they can relate. Although they have the ability to appreciate that their life may not be ideal, it is all that they have ever known and so they make do with things as they are. Parents of children with STC often comment that their child has only one friend and they do not actively socially interact with their peers. Whilst a parent may be terribly concerned by this, their child may simply be happy that at least they have a friend.

Interestingly it was not only in the study group that parents reported a poorer QoL than their child, with the parents of the control subjects also suggesting that their child had a worse QoL (Figure 15). Most QoL tools used in children are proxy reported in the belief than parents are well positioned to accurately judge the thoughts and feelings of their offspring. This study suggests that this is not the case, especially when psychosocial functioning is concerned and highlights the need for the use of self-assessment tools.

As previously mentioned, there are few studies that have sought to evaluate the quality of life in children with chronic constipation [265 273 277] and none in children with STC. The only studies concerning subjects with STC have concentrated on the effects of bowel resection in adults [265 273 277]. Jiang et al [266] describe a retrospective study comparing two different subtotal colectomy techniques, however they do not

include any pre-operative measurements of QoL and do not provide any control population. Similarly Riss et al [267] report solitary post-operative recordings of QoL in an observational follow-up study of 20 patients who have undergone colectomy at their institution. Reported post-procedure GLQI scores were diappointingly low, however of particular concern was the fact that only 6 of the study group (30%) fulfilled the Rome II criteria for constipation and 3 of their study group (15%) died in the peri-operative period. The authors do not recommend colectomy as a treatment for STC. Marchesi et al [268] also report GLQI scores post colectomy for adult subjects with STC and compare them with mean scores for 'healthy people'. They conclude that their technique does not appear to be '*inferior to others with regards to the overall impact on QoL*' but again fail to comment on any impact that solely having the condition STC might have on their subjects.

Asipu et al [265] looked at the effects of restorative proctocolectomy in children with severe childhood constipation. They describe the outcome in 5 children (mean age 12 years) who underwent transanal mucosal proctectomy, total abdominal colectomy (open (n=3) or laparoscopic (n=2)) and reconstruction with an ileal j-pouch-anal anastamosis. Prior to this all subjects had failed conventional medical management and had been left with an end stoma following unsuccessful attempted treatment with ACE procedures. One subject had an additional rectal resection early in life and one initially had their stoma unsuccessfully reversed prior to proceeding to restorative proctocoloectomy. All 5 subjects had transit studies performed with the results only available for 3 (138-146hrs). These figures suggest that these 3 subjects may have a diagnosis of STC (Beninga et al [19] use >100hrs to define STC). However, it is not

clear at what age or stage during their treatment the transit studies were performed (some subjects had additional surgical procedures that may have affected transit time) or more importantly the site of colonic delay (STC or FFR). All subjects were verbally satisfied with their decision to undergo surgery yet still had a mean GIQL score of 89 (55-127), with the quoted values in healthy volunteers being 126 (SD 13). Unfortunately due to the small numbers no statistical conclusions can be drawn from these figures and, as with the adult studies, no pre-operative data were recorded.

Faleiros et al [273] evaluated the health related QoL in children with functional defecatory disorders categorised according to the Rome II classification criteria [290]: functional constipation, functional faecal retention and non-retentive functional soiling. The QoL assessment questionnaire was a parent, proxy-reported generic instrument designed to assess both physical and psychosocial wellbeing [244]. The authors believe that parents' opinions are *'relevant and important'* and that they are *'able to estimate global wellbeing and behavioural changes'*. The results were compared to reference QoL scores for healthy controls.

The study found that parents of children with functional defecatory disorders reported a poorer QoL when compared to parents of healthy controls concerning both physical ($p<0.001$) and psychosocial ($p<0.001$) domains. When comparing the different subgroups, there was no recorded difference in psychosocial QoL however children with non-retentive functional soiling were reported as having significantly poorer physical QoL than those with functional constipation. The authors concluded that this was perhaps due to the higher incidence of soiling in this group (100% vs. 52%).

The current study found that physical QoL was affected by STC with scores significantly lower than controls in both child and parent-reported groups. A high proportion of the children in the study (41/51 - 80%) experienced soiling. This data would concur with the theorising of Faleiros et al that soiling adversely affects physical QoL [273].

The current study, however, found that parents of children, both STC and controls, reported significantly poorer quality of life than their child (figure 15 and 16). This perhaps suggests that parents are not as well positioned, as the authors believe, in estimating their child's QoL and that perhaps a more appropriate QoL tool could have been utilised.

Youssef et al [277] used the PedsQL QoL tool to investigate the impact of chronic constipation on QoL and also compared this result to scores they obtained from healthy control subjects recruited from a community-based general paediatric office (children who were attending '*for routine physical examination or receiving care for minor acute medical problems*'), children with a new diagnosis of inflammatory bowel disease (IBD) and gastro-oesophageal reflux disease (GORD). They defined chronic constipation as '*passing stools for >3 months and passage of fewer than 3 stools per week*'. They reported that children with chronic constipation described significantly lower QoL than those with IBD ($p<0.05$), GORD ($p<0.05$) and healthy controls ($p<0.05$) (mean scores 70.4 (SD 12.2), 83.8 (SD 13.2), 79.0 (SD 14.0) and 87.7 (SD 14.7) respectively). They also found that parents of children with chronic

constipation reported a significantly poorer QoL than their child ($p<0.05$, mean 60.0 (SD 18.4).

The study defines chronic constipation as difficulty passing stools for >3 months (straining, grunting, stool 'getting stuck') and passage of fewer than 3 stools per week citing Rasqin et al [290] (Rome II criteria) as their reference. The Rome II criteria define constipation in terms of Functional constipation (infants and preschool children), Functional faecal retention (infants to 16yrs, (i) passage of large diameter stools at intervals <2 times per week and (ii) retentive posturing, avoiding defecation by purposefully contracting the pelvic floor) and Functional non-retentive faecal soiling. The study population (5-18yrs) described by Youssef et al do not comply with the criteria in the reference either in terms of frequency of defecation or retentive posturing. The study group define the population as having 'chronic' symptoms presumably in keeping with the somewhat arbitrary definition of >3 months accepted by most investigators [291]. The QoL score was obtained at the initial gastrointestinal referral assessment before instigation of treatment. This differs from the population encountered in the current study who not only have proven delay in their colonic transit (STC), fulfil the Rome III criteria for functional constipation but who also have had refractory treatment resistant symptoms for a minimum of 2 years.

Whilst the current study also looks at the differences in reporting by parents in healthy controls as well as children affected by STC, Youssef et al concentrate solely on children with constipation. Their results suggest, as in the current study, that some of the difference seen in the parent-reported scores may be independent of disease

state (control child mean 87.7 (SD 14.7), control parent mean 80.7 (SD 15.1)) however there has been no formal statistical analysis.

One of the subgroups of children with constipation that the authors concentrate on are those who experience soiling. Only 29% of their study population experienced any problems with soiling - perhaps reflecting the differences in overall population in comparison to the current study. They did not find any difference in overall QoL when they compared children with constipation who soiled with those who did not. They did not specifically look at physical QoL in this group.

The authors, however, do concur with the current study that constipation appears to adversely affect both the physical and psychosocial functioning of children when compared to healthy controls and that the parents of affected children report poorer QoL scores in all domains.

There are several other studies that have used the PedsQL to assess HR-QoL in different populations; overweight/obese children [292], children with differing severity of cardiac disease [256], children with an acute orthopaedic injury [256], children with cerebral palsy, cancer or attention deficit hyperactivity disorder (ADHD) [260] and healthy children [256 259 260 292]. These previous results are summarised in Table 13 along with the results for the current study (in bold).

Table 15 - *Previous results for PedsQL questionnaire in different study populations.*

Population	Mean Child Reported Score			Mean Parent Reported Score		
	Total	Physical	Psychosocial	Total	Physical	Psycho-social
Healthy children [255]	79.6	80.2	79.3	80.9	81.4	80.6
Healthy children [259]	83.9	87.8	81.8	82.3	84.1	81.2
Healthy children [260]	84.3	88.0	82.3	79.9	81.8	78.9
Healthy children *	***86.0***	***92.1***	***83.3***	***84.3***	***92.8***	***79.7***
Not overweight	80.5	85.7	77.7	83.1	87.8	77.6
Overweight	79.3	83.5	77.0	80.0	82.6	76.1
Obese [292]	74.0	77.5	72.1	75.0	76.3	73.9
Orthopaedic (acute) [256]	78.1	75.3	79.5	73.7	72.7	74.3
Cardiac disease [256]						
- class Ia	83.6	82.1	84.5	86.5	89.5	84.6
- class IIb	75.9	78.7	74.3	80.1	82.8	78.5
- class III, IV	60.9	58.2	62.3	67.9	66.7	69.0
ADHD [260]	70.2	82.6	63.5	69.5	84.6	61.4
STC *	***72.9***	***78.8***	***69.2***	***64.4***	***74.4***	***58.6***
Cancer [260]	69.0	65.8	70.8	60.7	56.8	63.1
Cerebral Palsy [260]	66.3	64.8	67.0	56.3	53.3	57.9

In conclusion, this study shows that QOL is significantly lower in children with STC compared to normal children with both physical and psychosocial functioning scores reduced. Parental perception of QOL is worse when their child is affected by chronic constipation, particularly when estimating their child's psychosocial QOL.

6. Test-re-test reliability of nuclear transit studies to assess colonic transit time in children with slow transit constipation

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6. Test-re-test reliability of nuclear transit studies to assess colonic transit time in children with slow transit constipation

6.1 Introduction

Slow transit constipation (STC) is a condition characterised by global colonic delay that has been recognised as a cause of constipation in children since the 1990's [19 280 281 289]. It is characterised by intractable constipation that is not readily responsive to conventional treatment with patients often requiring surgical management involving bowel resection or appendicostomy formation [121 123 126-128 279 294-296]. Traditionally gastrointestinal transit time (GITT) has been quantified by radio-opaque marker studies. Following cessation of laxatives, subjects ingest capsules or food containing radio-opaque markers at the same time on consecutive days. Abdominal radiographs are taken at set intervals and the passage of the markers assessed [56-59].

Although marker studies are currently the most widely available tool for the assessment of GITT, there is significant doubt concerning their reproducibility, particularly in subjects with colonic inertia [57 61]. More recently, another method has been employed to investigate GITT, namely scintigraphy that is used to perform a nuclear transit study (NTS). Subjects are required to ingest foodstuffs, a small drink or capsules containing radiolabelled material (99m-Technetium or 67-Gallium citrate), then, scintigraphic images are obtained at requisite time intervals - usually 6, 24, 30 and 48hrs post ingestion [62-70]. The mean geometric centre (GC) of activity is calculated at each time point [134 297]. The GC is a number that represents the point where 50% of activity lies on either side. GC analysis has been validated and is

widely accepted as a means of assessing gastrointestinal transit [138]. One of the clear advantages of NTS is that they provide more detailed information on segmental transit. This is especially important if partial colonic resection is being considered.

Although colonic NTS's have been shown to have a satisfactory inter-observer reproducibility [298], little information exists concerning test-re-test reliability. Diagnoses, and subsequent surgical management decisions, are most commonly based on a solitary transit study. It is therefore essential that there be no doubt concerning the reliability of the information obtained by this single investigation. Ascertaining whether or not there is any appreciable difference in the results of nuclear transit studies performed on the same subject over time would aid in determining whether or not a solitary transit study is suffice.

There are no current studies that have sought to ascertain whether or not the results of NTS are reliably repeatable, particularly in the context of delayed colonic transit.

Success of management for STC is usually determined subjectively by symptom severity and individual patient satisfaction. Another way of assessing improvement would be to repeat a subject's colonic transit study. If the initial diagnosis has been made by scintigraphic evaluation then, in order to determine whether or not a difference in transit time is significant, it must first be established whether or not substantial test-re-test reliability exists.

6.2 Hypothesis and aim

This study hypothesises that NTS are a reliable means of reassessing colonic transit over time in children with STC. The aim of this study was to ascertain whether or not there is a measurable statistical difference in overall or segmental transit time in two studies performed at different time points in subjects where an initial NTS has demonstrated global colonic delay.

6.3 Materials and Methods

Children with symptoms of chronic constipation for >2 years who had undergone 2 separate nuclear transit studies to assess their gastrointestinal transit (where the first study in all cases had demonstrated slow colonic transit) were identified. In all children, on-going aggressive medical treatment (diet, laxatives, behavioural therapy) had failed to relieve their symptoms. These children were participating in a randomised controlled trial at a tertiary paediatric centre to evaluate the application of interferential electrical therapy (IFT) in the treatment of STC. The trial was assessing the efficacy of IFT versus placebo therapy. Some children required a repeat NTS prior to entry into the trial as they were required to have an up-to-date study (within the previous 2 years) in order to be eligible to participate. Other children had had 2 studies performed at their clinician's discretion. Subjects were instructed to keep to their normal diet and to cease their laxative medication for 5 days prior to commencing the study. If they were also having their gastric emptying assessed then they were instructed to fast for 4 hours on the day of the study.

Studies performed at RCH used 99m-Technetium colloid prior to 2000, and 67-Gallium citrate (5-20 MBq) after 2000, suspended in 20ml milk. The study performed at MMC used 67-Gallium citrate suspended in milk. The dose of tracer was determined according to each patient's weight and was based on an adult dose of 250 MBq. Anterior and posterior view images were obtained immediately after ingestion and during the subsequent 2 hours to estimate gastric emptying. Following this, patients were allowed to eat and drink as normal. Anterior view images were then collected at 6 +/- 1 (SD), 24 +/- 2, 30 +/- 2 and 48 +/- 2 hours from the time of ingestion.

The colon was divided into 6 separate regions of interest (ROI): 1 = Small bowel, 2 = Ascending colon, 3 = Transverse colon, 4 = Descending colon, 5 = Recto-sigmoid and 6 = Excreted. Each image was reviewed and the GC calculated. For each image, the fraction of administered activity in each ROI is multiplied by the region number (n) and then all are added to give the GC (a worked example is contained in section 1.15.2):

$$GC = \sum_{n}^{1} \text{fraction of activity in } ROI_n \times n$$

The GC at each time point for the initial and repeat studies were compared by parametric statistical analysis (paired t-test). A p-value of <0.05 was considered significant.

6.4 Results

In total, 7 children (4 male) had a NTS performed twice. The mean age at first study was 7.0 yrs (range 5.4-10.8 yrs), the mean age at second study was 11.4 yrs (range 9.7-14.2 yrs). The mean time between studies was 4.4 yrs (range 1-8.5 yrs).

13 of the 14 studies were performed at a single institute (Royal Children's Hospital (RCH), Melbourne) with the 14th study being performed at a sister hospital (Monash Medical Centre (MMC), Melbourne). Studies performed at RCH used 99m-Technetium colloid prior to 2000, and 67-Gallium citrate (5-20 MBq) after 2000. The study performed at MMC used 99m-Technetium colloid. GC were calculated for at 6, 24, 30 and 48hrs for the studies performed at RCH and 24 and 48hrs for the study performed at MMC due to the available raw data.

Qualitative visual assessment was performed on each image at each time interval to determine whether or not studies had similar overall appearances.

The mean GC and standard deviation (SD) at each time point for the first and second studies are shown in Table 16.

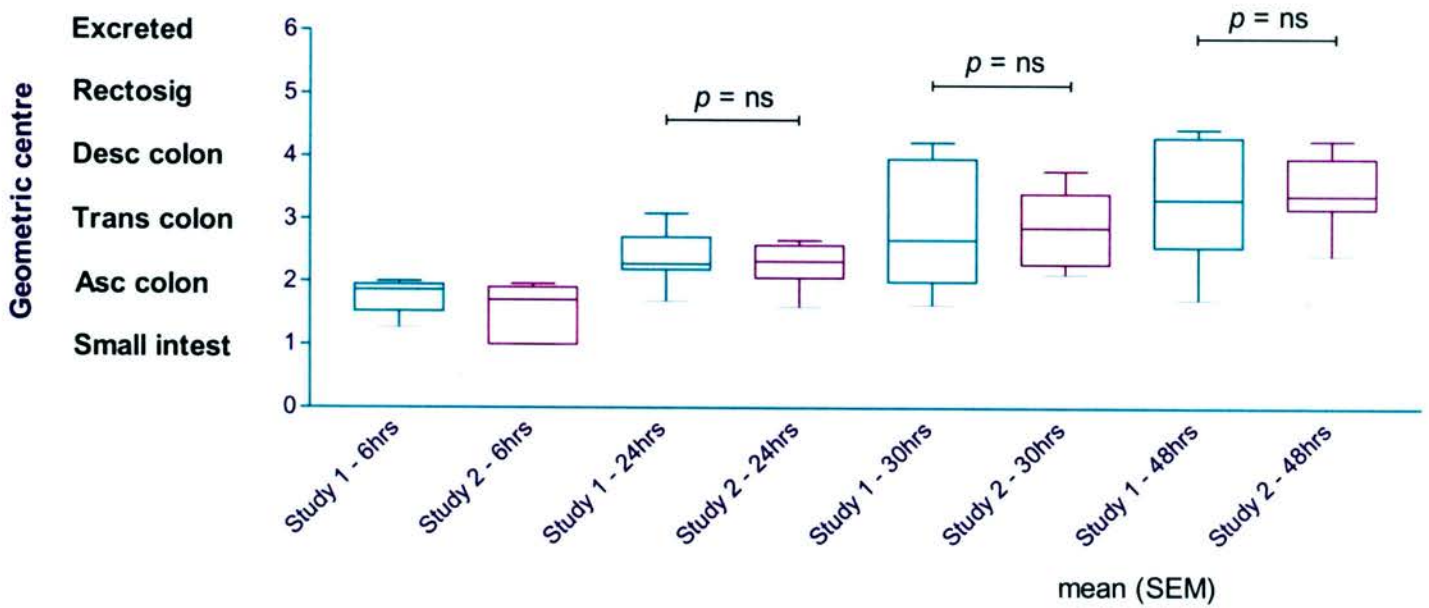

Figure 17 - *Comparison of geometric centres (GC) of activity using paired t-test for first and second nuclear transit studies at 6, 24, 30 and 48hrs post ingestion of radiolabelled material.*

Table 16 - *Mean geometric centres (GC) of activity for initial and repeat nuclear transit studies calculated at 6, 24, 30 and 48hrs post ingestion of radiolabelled material.*

	6hrs		24hrs		30hrs		48hrs	
	Mean	95%CI	Mean	95%CI	Mean	95%CI	Mean	95%CI
1st Study	1.78	1.5-2.06	2.30	1.92-2.68	2.88	1.89-3.87	3.20	2.30-4.10
2nd Study	1.54	1.09-1.99	2.23	1.90-2.56	2.85	2.26-3.45	3.39	2.86-3.92

For every child, the GC at each time point for both studies were compared by parametric statistical analysis using paired t-tests. There was no statistical difference in GC at 6hrs (mean + SD, 1.78 + 0.26 vs. 1.54 + 0.43; $p = 0.161$), 24hrs (mean + SD, 2.30 + 0.41 vs. 2.23 + 0.36; $p = 0.780$), 30hrs (mean + SD, 2.88 + 0.94 vs. 2.85 + 0.56; $p = 0.947$) and 48hrs (mean + SD, 3.20 + 0.98 vs. 3.39 + 0.57; $p = 0.615$) (Figure 17).

6.5 Discussion

This is the first study that has assessed the test-re-test reliability of nuclear scintigraphy in children with slow transit constipation. It has demonstrated that in a state of colonic inertia, NTS are reliably repeatable and can be relied on both as a diagnostic tool and perhaps subsequently as a means of assessing response to treatment. It is important to differentiate sufferers of STC from functional faecal retention (FFR) since it is now believed that the former represents an organic rather than a behavioural condition [19 20 280 299]. Consequently, treating children diagnosed with STC with behavioural modification and toileting regimes is for the most part ineffective and quite demoralising for the patient and family. Conversely, the

management of children with STC can require surgical intervention in the form of appendicostomy formation or even colonic resection.

Several studies have assessed the reproducibility of colonic NTS either alone or as part of other studies; however, those that have used nuclear scintigraphy have tended to concentrate on healthy individuals with much discrepancy in the time interval between repeat investigations.

Kamm et al [154] described a technique involving colonic intubation and subsequent instillation of both 99m-Technetium (in order to monitor colonic transit) and bisacodyl (to initiate colonic motor activity) in 1988. They evaluated this method on 6 healthy adults with one subject having 2 studies performed 2 days apart. They found that the second study gave similar results to the first.

McLean et al [142] assessed an oral colonic scintigraphic method in healthy adults using 111-Indium. Out of 41 subjects, 19 (10 female) underwent a repeat investigation, with a mean time between studies of 6 months (range 2-18 months). They assessed colonic motility in terms of total percent retention of the isotope (T%R) (expressed as a percentage of the activity in the colon at 6 hrs) and 'mean activity position' (MAP) (calculated as the GC of activity - where position 0 was at the caecum and position 99 was excreted activity) at 24, 48, 72 and 96 hrs. For T%R, the mean difference between the 2 studies at 24 and 48 hrs was less than 20% with this difference decreasing further with time. The mean difference in MAP was less than 15 at 24 hrs and decreased rapidly with time. The authors concluded that

their method demonstrated adequate reproducibility that was similar to that demonstrated for other nuclear medicine tests of gastrointestinal function.

Cremonini et al [138] also assessed the reproducibility of an oral colonic scintigraphic method in healthy adults using both 111-Indium and 99m-Technetium. Out of 37 subjects, 21 underwent a second study 3 weeks after the first. Gastric emptying, small bowel transit (colonic filling at 6 hrs) and colonic transit (GC calculation) were evaluated with images taken at 1, 2, 4, 24 and 48 hrs. Gastric emptying at 4 hrs showed the best reproducibility with only 14% of participants showing differences of more than 10% on repeat measurements (cf. ±10% difference for 70% of the data at 1 and 2 hrs). Variance in the percentage of colonic filling at 6 hrs was >10% in 45% of subjects. Colonic measurements varied by more than 1 GC unit in 37% of the subjects at 24 hrs and 26% of the subjects at 48 hrs. The authors acknowledged that with this method, gastric emptying showed greater reproducibility than both small bowel and colonic transit. However, they felt that compared to other studies looking at variability of gut transit in healthy individuals, the difference for some of the end points considered in their study was lower. Due to the natural variation in colonic transit even among healthy individuals, they also highlighted the need for further validation in relevant disease states.

Stubbs et al [137] investigated a method using non-digestible capsules containing 111-Indium to assess gastrointestinal transit in 10 healthy adults. Each subject had the study performed twice. The authors found that although the capsules could not be

considered as being chymous in nature, the colonic transit was highly reproducible in each subject and for the group as a whole.

Another study by Degen et al [300] looked at the variability in colonic transit in healthy adults but used both scintigraphy and marker studies in tandem. 32 subjects (12 female) had their gastrointestinal transit assessed on 2 occasions. Female subjects had the studies performed at identical phases in their menstrual cycle, and men had the studies performed 4 weeks apart. A study protocol using both 111-Indium and 99m-Technetium was used. Images were taken at 6, 24 and 48 hours and the GC of activity calculated. Radio-opaque markers were ingested for 3 days with a single abdominal radiograph taken on day 4. Repeated measurements of colonic transit showed mean results that were very reproducible with median differences of the GCs at 6 and 24 hrs very close to zero with narrow associated inter-quartile ranges. However, outliers were noted and the total ranges of inter-individual differences were wide with considerable variability in a few persons. The authors felt that as these differences were seen using both the scintigraphic and radio-opaque marker methods, they must reflect physiological changes in gut function rather than methodological artefacts.

Although a few studies have assessed the reproducibility of gastrointestinal transit studies in subjects with constipation [61 301] and irritable bowel syndrome [57] they have all used methods employing radio-opaque markers rather than nuclear scintigraphy. Instead, more studies have concentrated on looking at the reproducibility of studies comparing differing scintigraphic and radio-opaque marker methods [141 147 302].

The gold standard for assessing GITT is with radio-opaque marker studies. These can take the form of either a single [56 57 152 303] or multiple film study [58 131 152] with ingestion of either single or multiple markers. Although all methods have been shown to produce comparable results when total colonic transit time is evaluated [57] they each have their own limitations. Single film, single marker studies are unable to assess segmental transit, which is essential when evaluating colonic transit prior to potential colonic resection. Multiple film, single marker studies, provide important information regarding segmental transit time, but involve the subject being exposed to much larger doses of radiation. A technique has been described where multiple different markers are ingested for sequential days until a 'steady state' is achieved, then a solitary film acquired [56 57 149 152 303]. In the majority of studies this has been reported as a reliable technique for assessing segmental transit time in healthy non-constipated and constipated subjects in both adult [56 152 303] and child [149] populations. However, in one study analysing this method, although the authors report good evaluation of segmental and colonic transit time in control subjects, patients with hindgut dysfunction and patients with outlet obstruction, they estimate that in patients with colonic inertia subjects would have to ingest markers for 27 consecutive days in order to achieve a 'steady state' and be able adequately assess transit [57]. The authors also highlight that single film studies are unable to assess retrograde movement of markers which again can be an important physiological finding.

NTS have the advantage over radio-opaque marker studies that they allow accurate assessment of regional colonic transit with multiple images of the colon being easily obtained with a relatively low radiation dose [147]. In addition, in contrast to marker studies, overlapping regions of the gastrointestinal tract do not pose a problem when viewing sequential radio-isotope images. Some studies have suggested that there may be a difference between the passage of radioisotope and radio-opaque markers with the former possessing the ability to more accurately reflect the passage of physiological chyme. Stivland et al [304] found that markers were consistently faster in their transit through the right colon than radio-isotope. It has also been proposed that indigestible solid particles do not move with a meal, and may not be handled by the colon in the same manner as stool [61].

This study is hampered both by the small number of subjects (7 children) and the wide variation in timing between repeat investigations (1-8.5 yrs). Although unlike repeated x-ray studies NTS involve a low dose of radiation, there is a significant amount of patient time and cooperation involved and so there are few subjects in whom two studies have been performed. It could be argued that the fact that there appears to be good correlation between repeated results in spite of the wide variation in time between the two studies in fact strengthens the current findings. There will also discrepancy in the treatment received by each subject in the intervening time period between studies. It is interesting however, than laxative therapy does not appear to affect colonic transit time - certainly in these subjects who had experienced no subjective improvement in their symptoms. Metcalf et al [56], in shorter term studies assessing colonic total and segmental transit time in healthy adults using a

multiple marker single film technique, did not find that a small dose of supplemental fibre altered colonic transit time.

It must also be recognised that there are presently few centres that either have the ability to or choose to perform NTS and that radio-opaque marker studies remain the current gold standard for the assessment of colonic transit time.

In conclusion, the current study shows that NTS are a reliable means of reassessing global colonic transit and segmental colonic transit in children with slow transit constipation when repeated after a discernable time period.

7. Evaluation of transcutaneous electrical stimulation in the treatment of children with slow transit constipation [305 306]

7. Evaluation of transcutaneous electrical stimulation in the treatment of children with slow transit constipation

7.1 Introduction

Transcutaneous inferential therapy (IFT) is a non-invasive, painless means of delivering medium-frequency current electrical stimulation. To date its use has been limited to pain relief [180] and the treatment of urinary incontinence secondary to detrusor instability [307 308]. A pilot study by Chase et al [170] sought to ascertain the potential benefit of IFT in children with slow transit constipation. The authors noted that a reported side effect in a previous study was that of diarrhoea [309] and hypothesised that the diarrhoea might have occurred as a result of increased colonic motility. This observation lead them to theorise that the application of IFT in children with STC may either also result in diarrhoea and soiling or might potentially be able to overcome the slow colonic transit and remove the faecal impaction and its resultant bypass soiling. The subjects in the study (n=8) were recruited on the basis of either a nuclear transit study (that showed delayed colonic transit) or seromuscular biopsies (that showed a reduction in substance P - an excitatory neurotransmitter - levels). All subjects had experienced symptoms of constipation for a minimum of four years and had had exhaustive medical therapy (behavioural modification, laxatives). Three children had required formation of an appendicostomy via which they were receiving regular antegrade colonic enemas in order to attempt to achieve continence [170]. Subjects received treatment for twenty to thirty minutes, three times a week for nine to twelve sessions. The reported outcome measures were frequency of spontaneous defecation (a stool occurring in response to an urge to defecate), number of bowel washouts, medication usage and number of incidents of soiling (an

involuntary loss of faecal material into clothing). The authors reported increased frequency of defecation in six out of eight subjects and reduced soiling in seven out of the eight subjects. The improvements in defecation frequency were maintained for one month in five of the six subjects and up to 3 months in three subjects. In terms of reduced soiling, the effects were maintained up to three months in the same three subjects who experienced an increase in their defecation frequency. The authors concluded that although a placebo response was possible, due to the size and duration of response, the improvement in symptoms was most likely due to the application of IFT.

7.2 Hypothesis and aims

This study hypothesises that transcutaneous electrical stimulation (in the form of interferential therapy (IFT)) can increase bowel motility, and improve symptoms, in children with STC. The study aims to determine whether or not transcutaneous IFT can affect the symptoms of STC in children (frequency of defecation, soiling, and abdominal pain) and their colonic transit time (as measured by nuclear scintigraphy). It also seeks to measure the quality of life (QoL) of study participants before and after treatment with IFT.

7.3 Materials and Methods

7.3.1 Study design

The study is a prospective, single blind, randomised (1:1) controlled partial crossover trial with 7 intervals: (i) 4 weeks baseline, (ii) 4 weeks of real or placebo stimulation, (iii) 1st 4 weeks post-treatment, (iv) 2nd 4 weeks post-treatment (v) 4 weeks of real

stimulation, (vi) 1st 4 weeks post-treatment and (vii) 2nd 4 weeks post treatment. Further assessments were carried out at 6 and 12 month post-completion of the trial. The trial design timeline is shown in Figure 18.

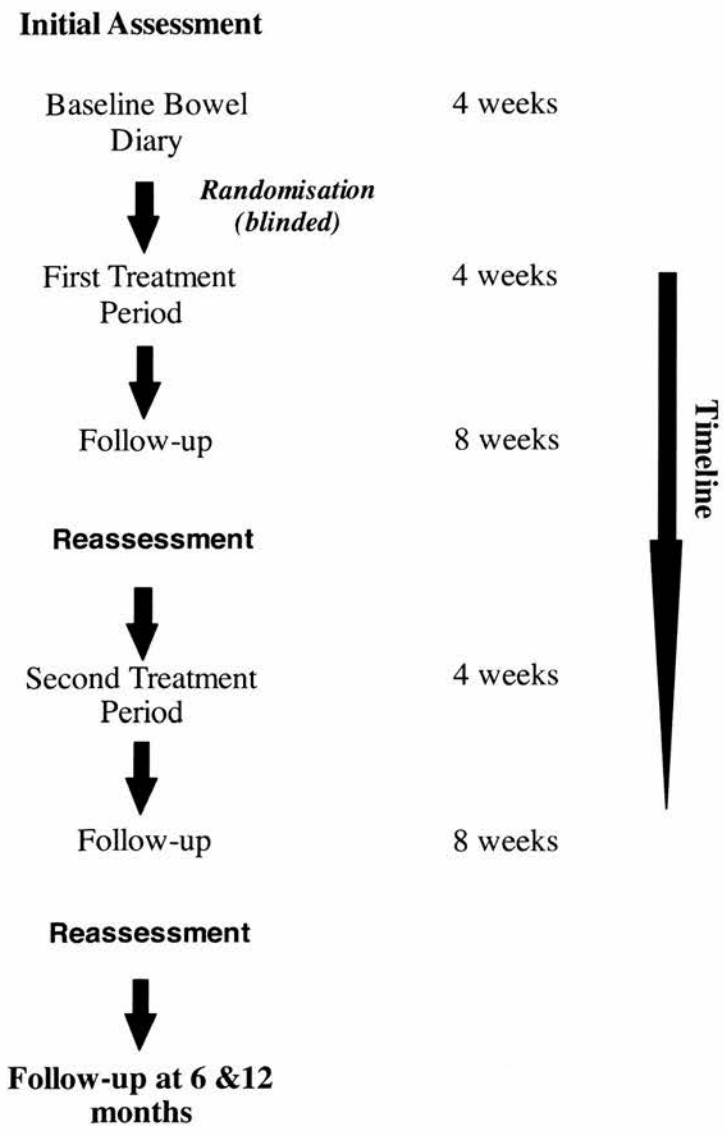

Figure 18 - *Timeline showing overview of trial design.*

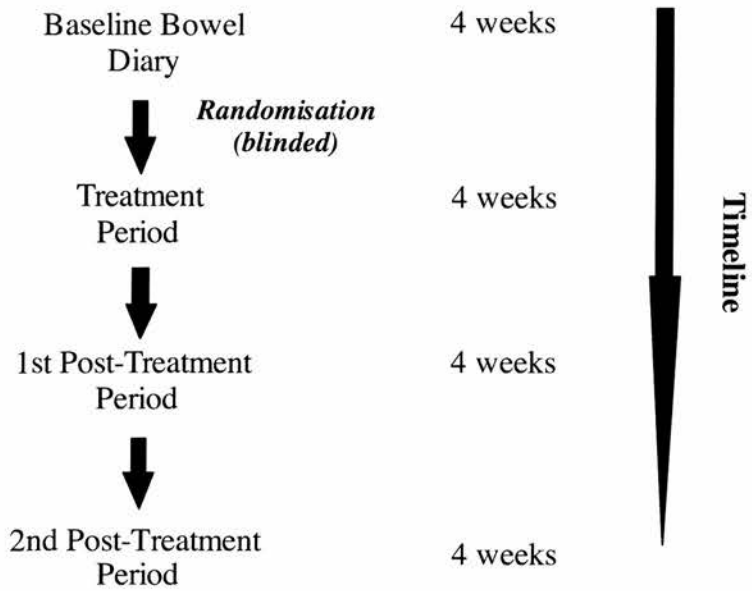

Figure 19 - *Timeline showing overview of reported study.*

This study reports the interim findings of the trial after a single treatment period the timeline of which is detailed in Figure 19. For the remainder of the chapter it is this timeline that should be referred to.

7.3.2 Participants

7.3.2.1 Inclusion criteria

- Children (aged 8-18 years) ≥2 year history of chronic constipation (consistent with Rome II criteria), +/- soiling, +/- appendix stoma (utilised for antegrade continence enemas).
- Blood tests to exclude hormonal, allergic and metabolic causes for their constipation (thyroid function tests (TFT), full blood count (FBC) and coeliac screen).

- Proven slow transit constipation on a recent (within the last 2 years) nuclear gastrointestinal transit study (scintigraphy).

7.3.2.2 Exclusion criteria

- Children with a normal colonic transit time or functional faecal retention (FFR) demonstrated on scintigraphy.
- Children with any metabolic or hormonal cause underlying their constipation.
- Children with HD or previous anorectal malformation.
- Children who have undergone any surgical procedure (other than the formation of an appendix stoma) that has resulted in discontinuity of their gastrointestinal tract.
- Children who have any contraindication to receiving transcutaneous electrical therapy (skin sensitivity, pacemaker *in situ*).
- Children who are unable to respond to the questionnaires due to intellectual disability or short attention spans.
- Previous transcutaneous electrical therapy for treatment of constipation.

7.3.2.3 Recruitment

Participants were primarily recruited from out-patient surgical and medical clinics at The Royal Children's Hospital (RCH), Melbourne. All health professionals (consultant gastroenterologists, consultant surgeons and paediatricians with an interest in continence) treating children with STC were made aware of the trial and were provided with recruitment fliers (Appendix 10). An advertisement (identical to the flyer) was also placed on the Paediatric Continence Association of Australia

(PCAA) website. If interested in participating in the trial, patients or their parents were encouraged to contact the trial coordinators and arrange an initial assessment. There was no unprecedented contacting of potential recruits by the trial coordinators.

7.3.3 Interventions

10 interferential machines (Vectorsurge 5 VS470, Metron Medical, Carrum Downs, Victoria, Australia) were purchased. 5 were returned to the manufacturer for modification. The machines were adapted so that although the dials read as though current was being delivered (i.e. lights came on and figures appeared in the digital panels) no actual stimulation was received by the patient. These machines were marked 'B' in a discrete place on their underside. The remaining 5 machines were marked 'A'.

The strategies employed to ensure effective blinding of both the trial coordinators and participants are discussed later.

7.3.3.1 Physiotherapist recruitment and instruction

Physiotherapists (n=26) located in the vicinity of each participant were recruited by the trial physiotherapist (Ms Janet Chase). Either the participant themselves, or the trial physiotherapist, identified potential practices which were then contacted and informed about the trial. If the physiotherapist was willing to participate in the trial then they were sent an information pack (Appendix 13). Each enrolled physiotherapist was visited by the trial physiotherapist prior to commencing any treatments. They were provided with 2 interferential machines (and appropriate

electrodes) and instructed on how to deliver therapy consistent with the trial protocol. At the end of each treatment period, the physiotherapist sent the invoice for the treatments to JC for appropriate reimbursement ($35 AU per treatment).

7.3.3.2 Stimulation regime/parameters

12 (20 minute) treatment sessions were performed over a 28 day period. In order for their data to be included in the final analysis, participants had to receive a minimum of 10 treatments in a 28 day period. They must have had no more than 4 treatments in any 7 day period (This is also detailed in appendix 13)

Machines were set to deliver 4 electrode interferential current with a carrier frequency of 4kHz and a beat frequency range of 80-150Hz at an intensity of ≤40 mA for a duration of 20 minutes. The vector rotation and surge options were switched off. Current was delivered via 4 self-adhesive conducting electrodes (40mm x 40mm, Verity Medical Ltd., Hampshire, England). 2 electrodes were placed paraspinally (T9-T12) with the paired electrode positioned diagonally opposite on the anterior abdominal wall below the costal margin.

7.3.4 Outcome measures

7.3.4.1 Primary outcome measure

Episodes of 'spontaneous' defecation (i.e. the stool was passed with an associated positive need to defecate).

7.3.4.2 Secondary outcome measures

Episodes of 'sit' defecation (i.e. the stool was passed whilst the child was participating in a timed sit on the toilet - often in association with a toilet training program).

Total episodes of defecation (i.e. both 'spontaneous' and 'sit' defecation episodes).

Episodes of 'stain' soiling (i.e. just a mark on the underpants).

Episodes of 'scrape' soiling (i.e. faecal matter had to be removed from the underpants before they could be washed).

Episodes of abdominal pain.

Quality of life (assessed by the PedsQL, Holschneider and Templeton QoL assessment tools).

Colonic transit time (assessed by nuclear transit study).

7.3.4.3 Measurements

7.3.4.3.1 Baseline data collection

Having expressed an interest in participating in the trial, and having contacted the trial coordinators, potential recruits were invited to attend an *initial assessment*. This took place at the Royal Children's Hospital and was conducted by our Paediatrician (Dr Susie Gibb [SG]), Physiotherapist (Ms Janet Chase [JC]) and Associate investigator (Miss Melanie Clarke [MC]).

The trial was explained to the family and they were provided with written and verbal information outlining the study (Patient and Parent Information Statements - Appendix 14 and 15). Eligibility to enrol in the trial was assessed (see

inclusion/exclusion criteria) and scintigraphic, blood and pathological results were reviewed. If the child was considered appropriate to enrol, and both child and family were willing, then they were asked to complete a consent form (included in the parent and participant information statements). Children over 12 years of age were given their own consent forms with competence to give consent being determined on an individual basis by the assessing team, all of whom were experienced practitioners. Consent forms were signed by the participant or their parent (mother or father) and witnessed by a trial coordinator (SG or MC). If a family were keen to enlist but required an additional investigation (i.e. missing blood test) then they were still enrolled in the trial and the investigation was performed during the baseline period before their child received their first treatment. Once they were enrolled in the trial, each participant was allocated a unique identifying trial number.

SG or MC, using a questionnaire developed as the Medical Assessment Data Sheet (Appendix 16), assessed each child's bowel function and performed a clinical examination. The examination consisted of height, weight, blood pressure (BP) and pulse rate (PR) measurements (the latter 2 were performed with the child both supine and erect due to a possible correlation between SCT and autonomic dysfunction) along with an abdominal examination, lower limb neurological examination and anal inspection (See Medical Assessment Data Sheet (Appendix 16) for further details). At the same visit JC assessed the child's muscular defecatory control by asking the child to demonstrate how they sat on the toilet and strained to empty [6]. If any correctable issues were highlighted (i.e. abnormal posturing, incorrect muscle contraction/relaxation, incorrect feet placement) then they were addressed

accordingly. In addition JC assessed rectal perception by asking the child to complete a visual analogue scale (Appendix 17). The visual analogue scale (VAS) consisted of a horizontal line, 100 mm in length, anchored by word descriptors (in this case describing rectal perception) at each end. The child placed a mark on the line at the point that they felt represented their perception of their current state. The VAS score was then determined by measuring in millimetres from the left hand end of the line to the point that the patient marked (score 0-100).

7.3.4.3.2 Bowel diary

Each child was provided with a Bowel Diary (Appendix 18). This was a daily record of bowel function, symptomatology and medication usage. Each participant, or their parent, was required to complete their bowel diary, every day, for the entire duration of the trial. Participants, and their family, were instructed at this initial consultation about how to fill in their diary and the importance of doing so. They documented the passage of any stool and whether or not it was passed 'spontaneously' (i.e. with an associated positive need to defecate) or was a 'sit' (i.e. the stool was passed whilst the child was sitting on the toilet often in association with a sitting toilet training program). The stool type, according to the Bristol Stool Scale (Appendix 19), was also recorded. In addition, any involuntary passage of stool, or 'soiling', was noted. Participants were asked to detail any episode of soiling and whether or not was a 'stain' (just a mark on the underpants) or a 'scrape' (faecal matter had to be removed from the underpants before they could be washed). In addition, any medicines or therapies received each day were recorded (both name and dosage). Finally, participants were asked to document whether or not they had any IFT treatment, or

'physio', and whether or not they experienced any abdominal discomfort or 'tummy pain'. There was an extra column where any additional information could be written (intercurrent illness, travel away from home etc...). The diary pages were colour coordinated dependent upon treatment period (blue for pre-treatment, red for the First Treatment Period, yellow for the following 8 weeks, purple for the Second Treatment Period and green for the final 8 weeks) and were provided to each participant in a waterproof folder. This folder also contained contact details for the trial coordinators.

The child was asked to create themselves a 'code name'. This was used on all of their documentation, along with their trial number, in order to maintain complete anonymity.

7.3.4.3.3 Quality of life

Quality of life was assessed by obtaining Holschneider (clinical evaluation of faecal incontinence) and Templeton (quantitative assessment of QOL) scores, and by completion of Pediatric Quality of Life Inventory 4.0 Generic Core Scale QOL questionnaires (PedsQL - Appendix 9, Holschneider and Templeton - Appendix 20). The PedsQL questionnaires consist of parallel child and parent self-report scales, and have been validated in children and adolescents aged 2-18. This study utilised the child (8-12yrs) and the teen (13-18yrs) questionnaires. Each questionnaire consists of 23 items encompassing (i) Physical functioning (8 items) (ii) Emotional functioning (5 items) (iii) Social functioning (5 items) and (iv) School functioning (5 items). The categories can then be grouped into Physical (i) and Psychosocial (ii, iii

& iv) functioning. The questions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilised (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse scored (0 =100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) and linearly transformed to a 0-100 scale (by adding all the scores together and dividing by the number of questions). Higher scores indicate better quality of life.

Parent and child completed the questionnaires independently with impartial assistance being provided by the trial coordinators for any child who had difficulty with comprehension.

Quality of life was assessed prior to entering into the trial and subsequently after completion of each treatment period.

7.3.4.3.4 Colonic transit time

Colonic transit time was measured using nuclear transit studies (see chapter 2 and chapter 6). Subjects were instructed to keep to their normal diet and to cease their laxative medication for 5 days prior to commencing the study. If they were also having their gastric emptying assessed then they were instructed to fast for 4 hours on the day of the study.

Studies performed prior to 2000 used 99m-Technetium colloid, and those after 2000 67-Gallium citrate (5-20 MBq), suspended in 20ml milk. The dose of tracer was determined according to each patient's weight and was based on an adult dose of 250 MBq. Anterior and posterior view images were obtained immediately after ingestion

and during the subsequent 2 hours to estimate gastric emptying. Following this, patients were allowed to eat and drink as normal. Anterior view images were then collected at 6 +/- 1 (SD), 24 +/- 2, 30 +/- 2 and 48 +/- 2 hours from the time of ingestion.

The colon was divided into 6 separate regions of interest (ROI): 1 = Small bowel, 2 = Ascending colon, 3 = Transverse colon, 4 = Descending colon, 5 = Recto-sigmoid and 6 = Excreted. Each image was reviewed and the GC calculated. For each image, the fraction of administered activity in each ROI is multiplied by the region number (n) and then all are added to give the GC (a worked example is contained in section 1.15.2):

$$GC = \sum_{n}^{1} \text{fraction of activity in } ROI_n \times n$$

Colonic transit was assessed prior to entry into the trial after subjects were invited to attend for reassessment following completion of each treatment period.

7.3.5 Sample size

7.3.5.1 Sample size estimation

Sample size was calculated using the outcome measure that changed the least in the pilot study [170] - defecation. During the study, 5/8 (63%) children increased defecation frequency from <3 into the normal range. It was expected that the placebo effect would be between 30-40%.

(i) *Comparing proportions - change in full treatment vs. placebo*

Given that the placebo effect is normally ~30%, and in the pilot study the treatment produced a change in 30% more children than the placebo, one can reasonably expected a greater than 10% change.

Using data from the pilot study where 5/8 (63%) children showed increased defecation: $\therefore p = 0.63, n = 8$

Where $SE^2 = p(1-p) / n$ *(SE = standard error)*

$= 0.63 (1-0.63) / 8$

$= 0.029$

and $SD^2 = SE^2 \times n$

$= 0.00084 \times 8$

$= 0.0067$

$SD = 0.082$

In order to see a change of >10% ($\delta = 0.1$) with a statistical significance of $p < 0.5$:

$n = 16 (SD^2 / \delta^2)$ *(δ =difference)*

$= 16 (0.0067 / 0.01)$

$= 10.72$

sample size = 2n = 22

$\therefore$ *22* patients are required to conclude a statistical difference ($p<0.05$) if the treatment produced changes in 10% more patients than the placebo.

7.3.5.2 Interim analysis

To ensure that excess participants are not studied, once >75% of participants have been recruited and completed their treatment it is the intent of the investigators to perform interim analysis in order to determine whether or not it is ethically appropriate to continue recruiting subjects into the trial.

7.3.6 Randomisation

Participants were randomised to either receive treatment A (real stimulation) or treatment B (placebo stimulation) for their First Treatment Period. Randomisation was in blocks of 6 according to age (8-12 and 13-18) in order to ensure even distribution of the 2 groups. Randomisation was performed by independent investigators (CP & AH). 6 cards, 3 labelled A and 3 labelled B, were shuffled and then the order recorded (i.e. 1=A, 2=A, 3=B, 4=B, 5=A, 6=B). This was repeated for each block of 6 until 60 numbers had letters assigned. Letters addressed to the treating physiotherapist stating to which treatment arm the participant had been randomised (Appendix 11) were placed in sealed, numbered envelopes. The envelopes were numbered sequentially from 1 to 60 with the contents of each envelope (treatment A or B) corresponding to the previously generated randomisation sequence. The list recording the number and contents of each envelope was not be seen by the trial coordinators and was stored in a separate locked office.

On entry into the trial each participant was given a trial number by the trial coordinators. The child's name and trial number were written on the outside of the

next envelope, and the envelope sent to the appropriate treating physiotherapist. Both the unique identifying trial number and envelope number were recorded in duplicate.

7.3.7 Blinding

The participants were informed that they would be receiving one of 2 levels of treatment. They were not told in which order they were to receive the treatment and so were blinded to their treatment. The trial coordinators were also blinded as to the treatment received by each participant. Only the treating physiotherapist was aware whether or not the child was receiving real or placebo treatment due to the legalities of applying a machine with/without live electric current to a patient. The physiotherapist was asked not to divulge the treatment information to any of the trial coordinators or the participants. In addition each physiotherapist recorded which machine (A or B) they used for each session on each participant and returned the recording sheets to an independent person (SD'C) for locked storage following the completion of each treatment period (Appendix 12).

Interferential stimulation is performed utilising cutaneous electrodes. Whilst the current is being delivered, a tingling sensation is felt in the skin underlying the electrode. In order to attempt to effectively blind the participants, physiotherapists delivering the treatment used a set dialogue independent of whether machine A (real) or machine B (placebo) was used. Participants were informed that as the machine was turned up they may or may not feel something and to let the treating physiotherapist know if they did. As all of the participants had never had any

electrical stimulation prior to entering into the trial, it was our hope that they would not have any preconceived idea about what they should be feeling. Physiotherapists were instructed to avoid discussing with the participant and their family how the treatment was affecting their symptoms.

7.3.8 Statistical analysis

7.3.8.1 Bowel symptom diary data

Data were separated into four 4 week (28 day) periods - (i) 4 weeks baseline, (ii) 4 weeks of real or placebo stimulation, (iii) 1st 4 weeks post-treatment, (iv) 2nd 4 weeks post-treatment. Events of defecation (spontaneous, sit and total), soiling (stain, scrape and total) and abdominal pain occurring per 4 week (28 day) period were divided by 4 to give number of events per week (7 days). These resultant figures were utilised for data analysis. Events/week occurring in the different data periods were compared between the two groups (real and placebo) and in a linear manner within each group for the study period. All data were tested for normality. Independent sample and paired *t* tests (two-tailed) were performed using Graphpad Prism Version 3.02. All p values < 0.05 were considered as statistically significant.

7.3.8.1.2 Missing data

In some cases data periods were incomplete due to a variety of reasons (lost diary pages, forgetting to complete diary, starting treatment period too early, dropping out of trial). In these cases, the number of known events in the treatment period were divided by the number of days of available data and then multiplied by 28 to give the expected number of events. This figure was then divided by 4 to provide the

expected number of events per week and this final figure was entered into the analysis. Where there was no available data for a treatment period, no data analysis could be performed.

7.3.8.2 Quality of life questionnaires

7.3.8.2.1 Peds QL scores

Parent-reported and child-reported physical, psychosocial and total quality of life scores pre- and post-intervention were compared between the two treatment groups before and after intervention and for each treatment group in a linear manner. All data were tested for normality. Independent sample and paired *t* tests (two-tailed) were performed using Graphpad Prism Version 3.02. All p values < 0.05 were considered as statistically significant.

7.3.8.2.2 Holschneider Templeton scores

Holschneider [310] incontinence and Templeton [271] quality of life scores were calculated for each participant pre- and post-intervention. Again, scores were compared between the two treatment groups before and after intervention and for each treatment group in a linear manner. All data were tested for normality. Independent sample and paired *t* tests (two-tailed) were performed using Graphpad Prism Version 3.02. Where the data were not normally distributed either Mann Whitney or Wilcoxon matched pairs testing was performed. All p values < 0.05 were considered as statistically significant.

7.3.8.3 Nuclear transit studies

Geometric centres (GC) of activity were calculated at 6, 24 and 48 hours for each study. Post intervention GC were compared between the placebo and real treatment groups. Pre- and post-intervention studies were also compared for each treatment group. All data were tested for normality. Independent sample and paired *t* tests (2-tailed) were performed using Graphpad Prism Version 3.02. All p values < 0.05 were considered as statistically significant.

7.4 Results

Between February 2006 and February 2008, 47 participants were recruited and randomised (see CONSORT 2010 Flow Diagram). Six potential participants volunteered to have colonic manometry performed and so were unable to be recruited (see Chapter 7). Another family declined to participate. 24 participants were randomised to receive real stimulation and 23 to receive placebo stimulation. Of these 47 subjects, 35 had usable bowel diary data for analysis. Of the remaining 12, 3 were found to ineligible (1 due to undisclosed previous surgery, 1 did not have slow colonic transit on further review of their nuclear transit study, 1 had an underlying undiagnosed condition), 2 dropped out (1 due to pre-existing psychological problems that required in-patient treatment in a psychiatric unit, 1 due to family issues resulting in a move away from the treating physiotherapist), 1 participant lost their bowel diary and 6 participants had incomplete data sets.

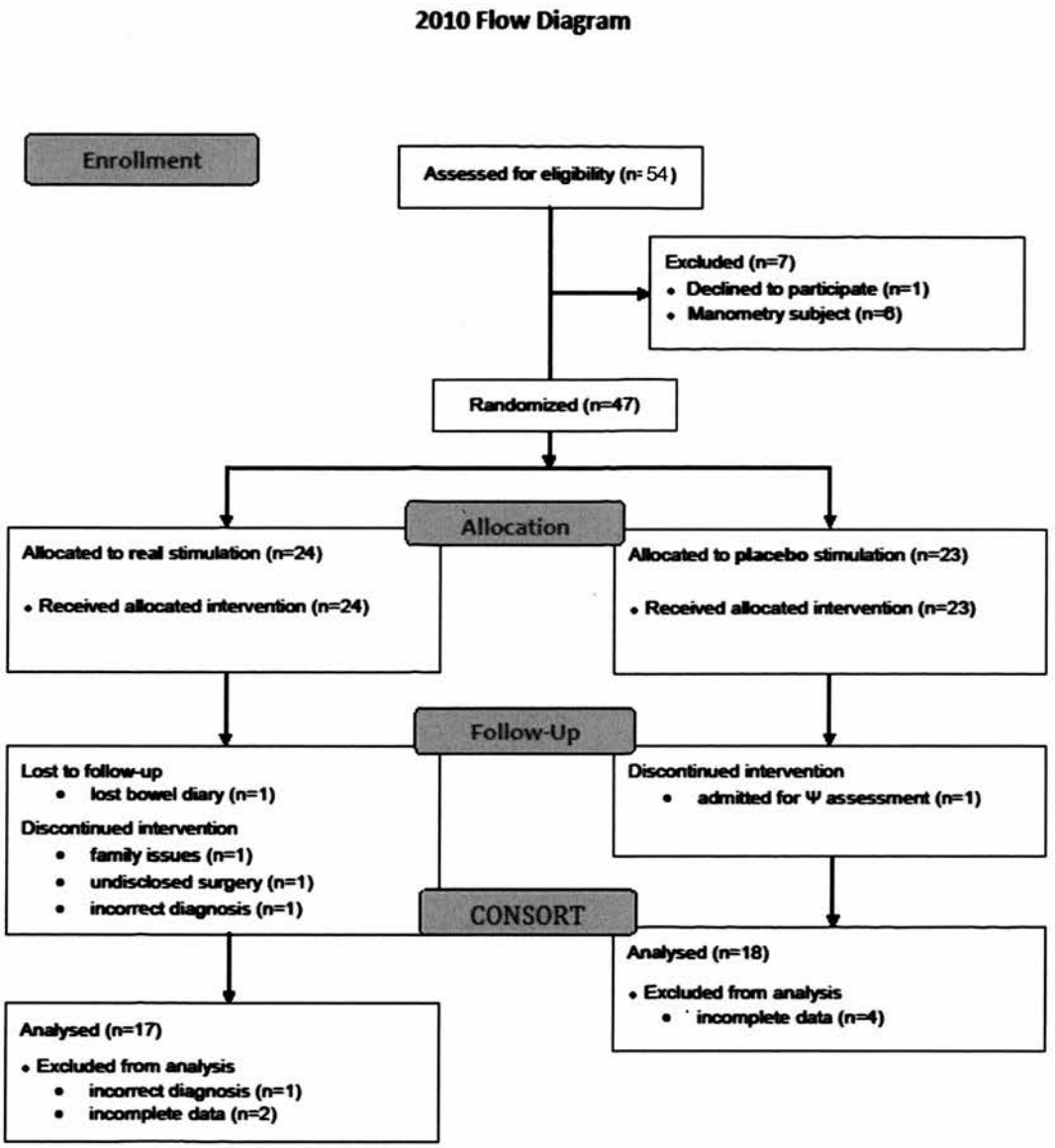

Figure 20 - *CONSORT 2010 Flow Diagram.*

Eight of the 35 data sets that were used for the interim results had 1-2 days missing from the 2nd post-First Treatment Period data. As previously stated, in these cases, the number of known events in the treatment period were divided by the number of days of available data and then multiplied by 28 to give the expected number of events. This figure was then divided by 4 to provide the expected number of events per week and this figure was entered into the analysis.

Table 17 - *Demographics of study population.*

	Placebo	**Real**
Number of children	18	17
Male:Female	1:1	1.8:1
Average age (yrs)	11.6	12.0
Male/Female (yrs)	11.1/12.0	12.1/11.8
Age range (yrs)	7.8-16.5	7.4-17.7
Average duration of symptoms (yrs)	8.6	10.5
Range of duration of symptoms (yrs)	2.7-14.4	4.4-13.9
Symptoms since birth	4/18	6/17
Abdominal pain	13/18	13/17
Average score /10	5.5	4.3
Soiling	16/18	13/17
Severe (daily/constant) soiling	12/16	10/13
Appendicostomy	2/18	3/17
Weight		
Underweight (BMI <5th centile)	0/18	1/17
Healthy (BMI 5-85th centile)	14/18	12/17
Overweight (BMI 85-95th centile)	4/18	2/17
Obese (BMI >95th centile)	0/18	2/17
Medication	16/18	12/17

Thirty-five children (20 male), mean age 11.8 years (range 7.4-17.7 years) with STC were analysed. Seventeen children received real IFT. There were no statistical

differences between the 2 groups concerning sex, age, onset/duration of symptoms, soiling and abdominal pain (Table 17).

7.4.1 Primary outcome measure

7.4.1.1 Frequency of 'spontaneous' defecation

The mean number of 'spontaneous' defecation episodes per week for each 28 day treatment period for both the real and placebo groups are shown in Table 18. All data sets demonstrated normal Gaussian distribution.

Table 18 - *Table showing episodes of 'spontaneous' defecation (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of 'spont' defecation /week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	3.00	3.14
	Treatment (4 weeks)	3.67	4.01
	1st post treatment (4 weeks)	3.54	3.96
	2nd post treatment (4 weeks)	2.97	3.12
PLACEBO (n=18)	Pre-treatment (4 weeks)	2.67	2.41
	Treatment (4 weeks)	3.35	2.52
	1st post treatment (4 weeks)	3.43	2.74
	2nd post treatment (4 weeks)	3.51	2.95

When comparing the real and placebo treatment groups, there was no difference in number of 'spontaneous' defecation episodes in the pre-treatment period (mean 3.00

vs. 2.67; $p = 0.73$). Following intervention, there remained no significant difference in the number of 'spontaneous' defecation episodes between the 2 groups during the treatment period (mean 3.67 vs. 3.35; $p = 0.77$) and during both the first post-treatment period (mean 3.54 vs. 3.43; $p = 0.92$) and second post-treatment periods (mean 2.97 vs. 3.51; $p = 0.60$).

Linear analysis was also performed for both treatment groups. In the real treatment group, there was no significant difference in episodes of 'spontaneous' defecation when comparing the pre-treatment period with treatment (mean 3.00 vs. 3.67; $p = 0.29$), first post-treatment (mean 3.00 vs. 3.54; $p = 0.33$) and second post-treatment (mean 3.00 vs. 2.97; $p = 0.96$) periods. In the placebo group there was no difference in episodes of 'spontaneous' defecation when comparing the pre-treatment and treatment (mean 2.67 vs. 3.35; $p = 0.14$) or first post-treatment (mean 2.67 vs. 3.43; $p = 0.13$) periods. There was, however, a significant difference when comparing the pre-treatment and second post-treatment periods (mean 2.67 vs. 3.51; $p = 0.03$).

7.4.2 Secondary outcome measures

7.4.2.1 Frequency of 'sit' defecation

The mean number of 'sit' defecation episodes per week for each 28 day treatment period for both the real and placebo groups are shown in table 19. All data sets demonstrated normal Gaussian distribution.

Table 19 - *Table showing episodes of 'sit' defecation (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of 'sit' defecation /week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	3.26	4.24
	Treatment (4 weeks)	2.90	4.10
	1st post treatment (4 weeks)	2.54	3.89
	2nd post treatment (4 weeks)	2.80	3.95
PLACEBO (n=18)	Pre-treatment (4 weeks)	2.83	3.31
	Treatment (4 weeks)	2.74	3.79
	1st post treatment (4 weeks)	2.40	3.60
	2nd post treatment (4 weeks)	2.11	2.64

When comparing the real and placebo treatment groups, there was no difference in number of 'sit' defecation episodes in the pre-treatment period (mean 3.26 vs. 2.83; p = 0.74). Following intervention, there remained no significant difference in the number of 'sit' defecation episodes between the 2 groups during the treatment period (mean 2.90 vs. 2.74; p = 0.90) and during both the first post-treatment period (mean 2.54 vs. 2.40; p = 0.91) and second post-treatment periods (mean 2.80 vs. 2.11; p = 0.54).

As with the primary outcome measure, linear analysis was also performed for both treatment groups. In the real treatment group, there was no significant difference in episodes of 'sit' defecation when comparing the pre-treatment period with the

treatment (mean 3.26 vs. 2.90; $p = 0.08$) and second post-treatment (mean 3.26 vs. 2.80; $p = 0.18$). There was a decrease in episodes of 'sit' defecation when comparing the pre-treatment and first post-treatment periods (mean 3.00 vs. 2.54; $p = 0.0004$). In the placebo group there was no difference in episodes of 'spontaneous' defecation when comparing the pre-treatment and treatment (mean 2.83 vs. 2.74; $p = 0.68$) or first post-treatment (mean 2.83 vs. 2.40; $p = 0.12$) periods. There was, however, a significant decrease in episodes of 'sit' defecation when comparing the pre-treatment and second post-treatment periods (mean 2.83 vs. 2.11; $p = 0.04$).

7.4.2.2 Frequency of 'total' defecation

The mean number of 'total' defecation episodes per week for each 28 day treatment period for both the real and placebo groups are shown in table 20. All data sets demonstrated normal Gaussian distribution.

Table 20 - *Table showing episodes of 'total' defecation (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of 'total' defecation /week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	6.26	4.96
	Treatment (4 weeks)	6.57	4.39
	1st post treatment (4 weeks)	6.09	4.69
	2nd post treatment (4 weeks)	5.78	3.45
PLACEBO (n=18)	Pre-treatment (4 weeks)	5.50	3.66
	Treatment (4 weeks)	6.08	3.87
	1st post treatment (4 weeks)	5.83	3.81
	2nd post treatment (4 weeks)	5.63	3.94

When comparing the real and placebo treatment groups, there was no difference in number of 'total' defecation episodes in the pre-treatment period (mean 6.26 vs. 5.50; $p = 0.61$). Following intervention, there remained no significant difference in the number of 'total' defecation episodes between the 2 groups during the treatment period (mean 6.57 vs. 6.08; $p = 0.73$) and during both the first post-treatment period (mean 6.09 vs. 5.83; $p = 0.86$) and second post-treatment periods (mean 5.78 vs. 5.63; $p = 0.83$).

When looking at the linear analysis for both treatment arms, there was no difference in 'total' number of episodes of defecation when comparing the pre-treatment period to any of the treatment/post-treatment periods.

7.4.2.3 Frequency of 'stain' soiling

The mean number of 'stain' soiling episodes per week for each 28 day treatment period for both the real and placebo groups are shown in table 21. All data sets demonstrated normal Gaussian distribution.

Table 21 - *Table showing episodes of 'stain' soiling (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of 'stain' soiling /week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	1.78	1.78
	Treatment (4 weeks)	1.57	1.66
	1st post treatment (4 weeks)	1.31	1.90
	2nd post treatment (4 weeks)	1.28	1.62
PLACEBO (n=18)	Pre-treatment (4 weeks)	2.10	1.90
	Treatment (4 weeks)	1.86	2.15
	1st post treatment (4 weeks)	1.67	1.88
	2nd post treatment (4 weeks)	1.57	1.90

When comparing the real and placebo treatment groups, there was no difference in number of 'stain' soiling episodes in the pre-treatment period (mean 1.78 vs. 2.10; $p = 0.61$). Following intervention, there remained no significant difference in the number of 'scrape' soiling episodes between the 2 groups during the treatment period (mean 1.86 vs. 1.57; $p = 0.66$) and during both the first post-treatment period (mean

1.31 vs. 1.67; $p = 0.58$) and second post-treatment periods (mean 1.28 vs. 1.57; $p = 0.63$).

As with the primary outcome measure, linear analysis was also performed for both treatment groups. In the real treatment group, there was no significant difference in episodes of 'stain' soiling when comparing the pre-treatment period with the treatment (mean 1.78 vs. 1.57; $p = 0.20$) and second post-treatment (mean 1.78 vs. 1.28; $p = 0.14$). There was a decrease in episodes of 'stain' soiling when comparing the pre-treatment and first post-treatment periods (mean 1.78 vs. 1.31; $p = 0.003$). In the placebo group there was no difference in episodes of 'stain' soiling when comparing the pre-treatment period with treatment (mean 2.10 vs. 1.86; $p = 0.63$), first post-treatment (mean 2.10 vs. 1.67; $p = 0.39$) and second post-treatment (mean 2.10 vs. 1.57; $p = 0.14$) periods.

7.4.2.4 Frequency of 'scrape' soiling

The mean number of 'scrape' soiling episodes per week for each 28 day treatment period for both the real and placebo groups are shown in table 22. All data sets demonstrated normal Gaussian distribution.

Table 22 - *Table showing episodes of 'scrape' soiling (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of 'scrape' soiling /week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	1.88	2.28
	Treatment (4 weeks)	1.38	1.54
	1st post treatment (4 weeks)	1.44	1.93
	2nd post treatment (4 weeks)	1.04	1.42
PLACEBO (n=18)	Pre-treatment (4 weeks)	0.83	1.10
	Treatment (4 weeks)	0.94	1.57
	1st post treatment (4 weeks)	1.44	2.19
	2nd post treatment (4 weeks)	1.24	2.17

When comparing the real and placebo treatment groups, there was no difference in number of 'scrape' soiling episodes in the pre-treatment period (mean 1.88 vs. 0.83; $p = 0.09$). Following intervention, there remained no significant difference in the number of 'scrape' soiling episodes between the 2 groups during the treatment period (mean 1.38 vs. 0.94; $p = 0.41$) and during both the first post-treatment period (mean 1.44 vs. 1.44; $p = 0.76$) and second post-treatment periods (mean 1.04 vs. 1.24; $p = 0.82$).

When looking at the linear analysis, in the real treatment group, there was a significant difference in episodes of 'scrape' soiling when comparing the pre-treatment period with the treatment (mean 1.88 vs. 1.38; $p = 0.05$) and second post-

treatment (mean 1.88 vs. 1.04; $p = 0.03$). There was no difference in episodes of 'scrape' soiling when comparing the pre-treatment and first post-treatment periods (mean 1.88 vs. 1.44; $p = 0.15$). In the placebo group there was no difference in episodes of 'scrape' soiling when comparing the pre-treatment period with treatment (mean 0.83 vs. 0.94; $p = 0.64$), first post-treatment (mean 0.83 vs. 1.44; $p = 0.10$) and second post-treatment (mean 0.83 vs. 1.24; $p = 0.21$) periods.

7.4.2.5 Frequency of 'total' soiling

The mean number of 'total' soiling episodes per week for each 28 day treatment period for both the real and placebo groups are shown in table 23.

Table 23 - *Table showing episodes of 'total' soiling (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of 'total' soiling /week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	3.66	3.34
	Treatment (4 weeks)	2.96	2.75
	1st post treatment (4 weeks)	2.75	3.13
	2nd post treatment (4 weeks)	2.32	2.41
PLACEBO (n=18)	Pre-treatment (4 weeks)	2.93	2.18
	Treatment (4 weeks)	2.81	2.51
	1st post treatment (4 weeks)	3.11	2.96
	2nd post treatment (4 weeks)	2.81	2.96

All data sets demonstrated normal Gaussian distribution.

When comparing the real and placebo treatment groups, there was no difference in number of 'total' soiling episodes in the pre-treatment period (mean 3.66 vs. 2.93; p = 0.45). Following intervention, there remained no significant difference in the number of 'total' soiling episodes between the 2 groups during the treatment period (mean 2.96 vs. 2.81; p = 0.87) and during both the first post-treatment period (mean 2.75 vs. 3.11; p = 0.73) and second post-treatment periods (mean 2.32 vs. 2.81; p = 0.60).

When looking at the linear analysis, in the real treatment group, there was a significant difference in episodes of 'total' soiling when comparing the pre-treatment period with the treatment (mean 3.66 vs. 2.96; p = 0.003), first post-treatment (mean 3.66 vs. 2.75; p = 0.03) and second post-treatment periods (mean 3.66 vs. 2.32; p = 0.02). In the placebo group there was no difference in episodes of 'total' soiling when comparing the pre-treatment period with treatment (mean 2.93 vs. 2.81; p = 0.83), first post-treatment (mean 2.93 vs. 3.11; p = 0.76) and second post-treatment (mean 2.93 vs. 2.81; p = 0.79) periods.

7.4.2.6 Frequency of abdominal pain

The mean number of episodes of abdominal pain per week for each 28 day treatment period for both the real and placebo groups are shown in table 24. All data sets demonstrated normal Gaussian distribution.

Table 24 - *Table showing episodes of abdominal pain (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Number of episodes of abdominal pain/week	
		Mean	SD
REAL (n=17)	Pre-treatment (4 weeks)	2.12	1.76
	Treatment (4 weeks)	1.37	1.44
	1st post treatment (4 weeks)	1.06	1.25
	2nd post treatment (4 weeks)	0.60	0.73
PLACEBO (n=18)	Pre-treatment (4 weeks)	2.14	2.12
	Treatment (4 weeks)	1.89	2.22
	1st post treatment (4 weeks)	1.51	2.06
	2nd post treatment (4 weeks)	1.81	2.37

When comparing the real and placebo treatment groups, there was no difference in number of episodes of abdominal pain in the pre-treatment period (mean 2.12 vs. 2.14; $p = 0.97$). Following intervention, there remained no significant difference in the number of episodes of abdominal pain between the 2 groups during the treatment period (mean 1.37 vs. 1.89; $p = 0.42$) and during the first post-treatment period (mean 1.06 vs. 1.51; $p = 0.44$). There was however a trend towards significance in episodes of abdominal pain when comparing the second post-treatment periods (mean 0.60 vs. 1.81; $p = 0.05$).

When looking at the linear analysis, in the real treatment group, there was a significant difference in episodes of abdominal pain when comparing the pre-

treatment period with the treatment (mean 2.12 vs. 1.37; p = 0.007), first post-treatment (mean 2.12 vs. 1.06; p = 0.0006) and second post-treatment periods (mean 2.12 vs. 0.60; p = 0.0007). In the placebo group there was no difference in episodes of abdominal pain when comparing the pre-treatment period with treatment (mean 2.14 vs. 1.89; p = 0.30) and second post-treatment (mean 2.14 vs. 1.81; p = 0.33) periods. There was a difference when comparing the pre-treatment and first post-treatment (mean 2.93 vs. 1.51; p = 0.05) periods.

7.4.2.7 Quality of life scores

Table 25 - *Demographics of study population.*

	Placebo	**Real**
Number of children	17	16
Male:Female	1.4:1	2.2:1
Average age (yrs)	11.4	12.1
Male/Female (yrs)	10.6/12.6	12.1/12.2
Age range (yrs)	7.8-16.5	7.4-17.7
Average duration of symptoms (yrs)	8.5	10.6
Range of duration of symptoms (yrs)	2.7-14.4	4.4-15.1
Symptoms since birth	4/17	6/16
Abdominal pain	14/17	12/16
Average score /10	5.5	4.1
Soiling	15/17	12/16
Severe (daily/constant) soiling	10	10
Appendicostomy	2/17	3/16
Weight		
Underweight (BMI <5th centile)	0/17	1/16
Healthy (BMI 5-85th centile)	11/17	11/16
Overweight (BMI 85-95th centile)	5/17	2/16
Obese (BMI >95th centile)	1/17	2/16
Medication	15/17	11/16

Quality of life data are available for thirty-three children (21 male), mean age 11.8 years (range 7.4-16.5 years). Sixteen received real IFT. There were no statistical differences between the 2 groups concerning sex, age, onset/duration of symptoms, soiling and abdominal pain (Table 25).

7.4.2.7.1 Peds QL quality of life scores

The parent and child reported mean QoL scores for both the real and placebo groups before and after intervention are shown in tables 26 and 27. All data sets demonstrated normal Gaussian distribution.

Table 26 - *Parent reported PedsQL scores (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Total QoL score		Physical QoL score		Psychosocial QoL score	
		Mean	SD	Mean	SD	Mean	SD
REAL	Pre-treatment	70.3	20.13	81.3	14.30	64.5	24.97
	Post-treatment	70.0	14.00	79.3	15.44	65.1	18.60
PLACEBO	Pre-treatment	69.8	13.84	79.6	13.37	63.8	18.90
	Post treatment	70.2	14.69	79.6	14.91	65.2	18.12

Parent reported scores - when comparing the real and placebo groups, there was no difference in pre-treatment total (mean 70.3 vs. 69.8; $p = 0.93$), physical (mean 81.3 vs. 79.6; $p = 0.73$) and psychosocial (mean 64.5 vs. 63.8; $p = 0.93$) QoL scores. Following intervention, there remained no difference in total (mean 70.0 vs. 70.2; $p = 0.97$), physical (mean 79.3 vs. 79.6; $p = 0.96$) and psychosocial (mean 65.1 vs. 65.2; $p = 0.99$) QoL scores.

Table 27 - *Child reported PedsQL scores (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Total QoL score		Physical QoL score		Psychosocial QoL score	
		Mean	SD	Mean	SD	Mean	SD
REAL	Pre-treatment	72.9	16.86	76.4	14.93	71.0	19.18
	Post-treatment	81.1	14.17	86.3	11.35	78.3	16.66
PLACEBO	Pre-treatment	74.9	8.24	85.3	8.17	69.0	10.45
	Post treatment	78.1	11.35	85.1	8.16	74.4	16.17

When performing linear analysis, there was no difference in parent reported QoL in the real treatment group after intervention for total (mean 70.3 vs. 70.0; $p = 0.93$), physical (mean 81.3 vs. 79.3; $p = 0.63$) and psychosocial (mean 64.5 vs. 65.1; $p = 0.86$) scores. This was also true for the placebo pre-and post-treatment total (mean 69.8 vs. 70.2; $p = 0.90$), physical (mean 79.6 vs. 79.6; $p = 0.99$) and psychosocial (mean 63.8 vs. 65.2; $p = 0.70$) scores.

Child reported scores - when comparing the real and placebo groups, there was no difference in pre-treatment total (mean 72.9 vs. 74.9; $p = 0.67$) and psychosocial (mean 71.0vs. 69.0; $p = 0.71$) QoL scores. There was however a difference in reported physical QoL scores (mean 76.4 vs. 85.3; $p = 0.04$). Following intervention, there remained no difference in total (mean 81.1 vs. 78.1; $p = 0.51$) and psychosocial (mean 78.3 vs. 74.4; $p = 0.50$) QoL scores. There was no difference in post-treatment child-reported physical QoL scores (mean 86.3 vs. 85.1; $p = 0.72$).

When performing linear analysis, there was a difference in child reported QoL in the real treatment group after intervention for total (mean 72.9 vs. 81.1; $p = 0.005$),

physical (mean 76.4 vs. 86.3; $p = 0.003$) and psychosocial (mean 71.0 vs. 78.3; $p = 0.02$) scores. There was no difference in child-reported placebo pre-and post-treatment total (mean 74.9 vs. 78.1; $p = 0.12$), physical (mean 85.3 vs. 85.1; $p = 0.93$) and psychosocial (mean 69.0 vs. 74.4; $p = 0.06$) scores.

7.4.2.7.2 Holschneider and Templeton quality of life scores

The mean Holschneider and Templeton QoL scores for both the real and placebo groups before and after intervention are shown in table 28. All data sets (apart from Templeton scores post intervention in the real treatment group) demonstrated normal Gaussian distribution.

Table 28 - *Holschneider and Templeton scores (mean + SD) for both treatment arms pre- and post- intervention.*

Treatment group	Treatment period	Holschneider score		Templeton score	
		Mean	SD	Mean	SD
REAL	Pre-treatment	8	2.37	2.5	0.56
	Post-treatment	10	1.45	2.5	0.40
PLACEBO	Pre-treatment	7	2.76	2.5	0.50
	Post treatment	9	2.42	2.5	0.39

When comparing the real and placebo groups, there was no difference in pre-treatment Holschneider (mean 8 vs. 7; $p = 0.56$) or Templeton (mean 2.5 vs. 2.5; $p = 0.63$) QoL scores. Following intervention, there remained no difference in Holschneider (mean 10 vs. 9; $p = 0.15$) or Templeton (mean 2.5 vs. 2.5; $p = 0.74$) QoL scores.

When performing linear analysis, there was a difference in Holschneider QoL scores following both real (mean 8 vs. 10; $p = 0.01$) and placebo (mean 7 vs. 9; $p = 0.02$) intervention. There was no difference in Templeton QoL scores following either real (mean 2.5 vs. 2.5; $p = 0.30$) or placebo (mean 2.5 vs. 2.5; $p = 0.11$) intervention.

7.4.2.7 Nuclear transit studies

Nuclear transit study data are available for twenty four children (14 male), mean age 12.0 years (range 7.4-17.7 years). Fifteen received real IFT.

Table 29 - *Demographics of study population.*

	Placebo	**Real**
Number of children	9	15
Male:Female	1.25:1	1.5:1
Average age (yrs)	11.7	12.2
Male/Female (yrs)	11.3/12.2	12.4/11.8
Age range (yrs)	7.8-16.5	7.4-17.7
Average duration of symptoms (yrs)	9.1	10.1
Range of duration of symptoms (yrs)	5.2-14.4	4.4-15.1
Symptoms since birth	3/9	3/15
Abdominal pain	6/9	11/15
Average score /10	5	4
Soiling	7/9	10/15
Severe (daily/constant) soiling	5/7	8/10
Appendicostomy	1/9	2/15
Weight		
Underweight (BMI <5th centile)	0/9	1/15
Healthy (BMI 5-85th centile)	7/9	10/15
Overweight (BMI 85-95th centile)	2/9	2/15
Obese (BMI >95th centile)	0/9	2/15
Medication	8/9	12/15

There were no statistical differences between the 2 groups concerning sex, age, onset/duration of symptoms, soiling and abdominal pain (Table 29).

Twenty eight studies were identified (2 subjects in each group had 2 pre-treatment studies performed). The mean GC at 6, 24, 30 and 48 hours with 95% confidence intervals for pre-treatment studies and pot-treatment studies in both treatment arms are shown in table 30. All data sets demonstrated normal Gaussian distribution.

Table 30 - *Mean geometric centres (GC) of activity for pre- and post-intervention nuclear transit studies calculated at 6, 24, 30 and 48hrs post ingestion of radiolabelled material.*

	6hrs		24hrs		30hrs		48hrs	
	Mean	95%CI	Mean	95%CI	Mean	95%CI	Mean	95%CI
PreRx	1.69	1.54-1.84	2.41	2.24-2.58	2.80	2.55-3.05	3.40	3.11-3.69
Placebo	1.64	1.37-1.91	2.52	2.31-2.72	2.71	2.31-3.11	3.10	2.58-3.62
Real	1.81	1.59-2.03	3.05	2.80-3.30	3.47	3.04-3.89	4.24	3.75-4.73

Post treatment GC at 6, 24, 30 and 48 hours were compared between the placebo and real intervention groups. There was no difference between the GC for the post-treatment placebo and real studies at 6 hours (mean +/- SEM - 1.64 +/- 0.12 vs. 1.81 +/- 0.10; $p = 0.28$). There was a significant difference in the post-intervention GC between the 2 treatment arms at 24 (mean +/- SEM - 2.52 +/- 0.09 vs. 3.05 +/- 0.12; $p = 0.004$), 30 (mean +/- SEM - 2.71 +/- 0.17 vs. 3.47 +/- 0.20; $p = 0.02$) and 48 (mean +/- SEM - 3.10 +/- 0.23 vs. 4.24 +/- 0.23; $p = 0.002$) hours.

When comparing the pre- and post-intervention studies, for the group who received real therapy, there was a significant difference in GC at 24 (mean +/- SEM - 2.53 +/- 0.12 vs. 3.05 +/- 0.11; $p = 0.001$), 30 (mean +/- SEM - 2.92 +/- 0.13 vs. 3.47 +/- 0.20; $p = 0.04$) and 48 (mean +/- SEM - 3.48 +/- 0.17 vs. 4.28 +/- 0.21; $p = 0.004$) hours. This was not so for the placebo group where statistical significance was not reached at any time point.

7.5 Discussion

Slow transit constipation in children represents a chronic medical condition that is refractory to current medical treatment. Interferential therapy is a non-invasive, transcutaneous form of electrical stimulation that is commonly used by physiotherapists for the treatment of bladder instability. Since electrical therapy is not widely used in current medical practice, and it's mechanism of action is poorly understood, placebo-intervention trials are recommended to confirm the validity of any perceived improvement. This chapter reports the interim results of a randomised controlled blinded placebo-partial crossover trial assessing the application of IFT in the treatment of children with STC.

Analysis of the results comparing the placebo and real treatment groups post intervention show that treatment of subjects with STC with IFT does not affect the defecation frequency ('spontaneous' and 'sit' defecation) or soiling frequency ('stain' and 'scrape' soiling). However, there was a reduction in the episodes of abdominal pain in the group who received real therapy in the second post-treatment period ($p = 0.05$). When directly comparing the real and placebo groups, there was

no measurable effect on quality of life when evaluated by PedsQL (parent and child reported), Holschneider or Templeton QoL tools. There does appear to be a decrease in colonic transit time quantified by nuclear scintigraphy following treatment with real IFT (24hrs $p = 0.004$, 30hrs $p = 0.02$, 48hrs $p = 0.002$).

When comparing data in a linear manner in each treatment arm, there is again no difference in defecation frequency in either group. There does appear to be a reduction in soiling (total soiling in all post treatment periods $p = 0.003$, 0.03 and 0.02) in the group that received real therapy. This is not so for the placebo group. The data also shows that there is an improvement in episodes of abdominal pain (all post treatment periods $p = 0.007$, 0.0006 and 0.0007) in the participants that received real treatment. When looking at the QoL data, there was no difference in parent-reported PedsQL scores in either treatment group. There was however a significant improvement in child-reported total ($p = 0.005$), physical ($p = 0.003$) and psychosocial ($p = 0.02$) scores in the real intervention group. There was an improvement in the colonic transit in participants who had received real treatment (24hrs $p = 0.001$, 30hrs $p = 0.04$, 48hrs $p = 0.004$) but not in those who had been given placebo therapy.

The current study sought to ascertain whether or not IFT was able to increase the defecation frequency in children with STC and as such was unable to demonstrate any improvement. It is, however, strikingly apparent that some children with STC do not display the defecation pattern normally associated with constipation of infrequent passage of stools [10]. Some of the subjects in the study reported pre-

intervention stool frequency of >2 or more defecations in the toilet per week. Children with STC often pass soft, putty like stool that is both difficult to pass and subsequently to wipe away. What is unknown, and difficult to quantify, is the volume of stool that is being passed on each occasion. Along with a record of each time they defecated, participants were also asked to record the consistency of their stool in accordance with the Bristol stool scale. Anecdotal analysis of this data suggested that there was an improvement in stool consistency despite there being no difference in frequency of defecation.

One of the most distressing symptoms associated with STC is the uncontrollable passage of stool. This can result either in a small mark on the underpants, a 'stain', or an amount of stool in the underwear that needs to be physically removed, a 'scrape'. It is thought that the soiling associated with STC is a major contributing factor to sufferer's poor quality of life [278]. Comparison of the placebo and real treatment groups did not demonstrate any improvement in soiling post-intervention. When looking at the linearly analysed data, following treatment with real IFT, there was a decrease in total episodes of soiling in all post treatment periods. The episodes of 'scrapes' were reduced during the treatment and second post-treatment periods with the 'stains' reduced in the first post-treatment period. There was no difference in either episodes of stains or scrapes in the placebo group.

The current study found that there was improvement in episodes of abdominal pain following treatment with real IFT. This was apparent in the second post-treatment period when directly comparing the real and placebo groups, and in all treatment

periods when looking at the linear analysis for the real intervention group. For some children abdominal pain is the most debilitating symptom associated with their constipation and results in many days off school. It was these children that seemed to have the most significant decrease in their pain. Interestingly, there were a few children for whom the episodes of abdominal pain appeared to increase. On further questioning, it became apparent that it was actually a need to defecate that these children were experiencing however, since it was a novel sensation, it was perceived as a painful stimulus. The meaning of this sensation was explained to subjects and they were encouraged to attempt to defecate when they felt they were experiencing 'pain'.

The study found that although there was no difference in child reported PedsQL QoL scores when comparing the post intervention real and placebo groups, there was a significant improvement in child self-perceived QoL when looking at the group who received real interferential therapy ($p = 0.005$). This was not so after placebo therapy. This improvement was apparent when examining both the physical ($p = 0.003$) and psychosocial ($p = 0.02$) aspects of their QoL.

Questions in the psychosocial domain mainly concentrate on getting along with other children, being teased and keeping up with peers. Children who experience faecal soiling are often shunned by their classmates, and so any improvement in this will undoubtedly improve their social acceptance and minimise any taunting. Interestingly, although children in the study for the most part have no outward physical disability, their QoL answers suggest that they feel that they are unable to

keep up with, and perform to the same standards, as their peers. This perceived gap appears to narrow following treatment with real IFT with significant improvement in physical QoL scores.

There was no improvement in parent-reported QoL following treatment with either real or placebo IFT when looking at the data comparing the treatment arms or within each intervention group. It is common for children with STC to have had defecatory problems from birth. When a parent has been living with a child with a chronic condition for so long, it may take longer than a few weeks of improvement for them to experience a change in mindset when considering the QoL of their child. Whereas a child has the ability to take an improvement in their condition at face value, an adult is more likely to be sceptical and need longer to accept that things have indeed changed.

In terms of clinical significance, when looking at the real IFT group, in the second post-treatment period the number of episodes of soiling decreased from a mean of 3.66/wk to 2.32/wk and the episodes of abdominal pain from a mean on 2.12/wk to 0.60/wk. This means that in a 28 day period, children experienced an average of 6 fewer days with soiling episodes (15/28 vs. 9/28) and 6 fewer days with abdominal pain (8/28 vs. 2/28). Although children are still clearly symptomatic, this small improvement, when considered in association with the chronicity of their symptoms, may feel like there's 'light at the end of the tunnel' and account for the improvement in child-reported QoL in the real intervention group. These findings, over a

relatively short period of time, certainly suggest that further evaluation of IFT as a treatment modality is warranted.

This study demonstrates that transcutaneous electrical treatment with IFT is effective in reducing colonic transit time, as measured by nuclear scintigraphy at 6-8 weeks after treatment, in children with STC. Their colonic transit times at 24, 30 and 48 hours were significantly decreased. This was not so when placebo IFT was administered and the transit study repeated. This is an objective measure and suggests that interferential therapy may have the ability to alter colonic motility. There were, however, a limited number of studies available with only 18 of the 35 participants attending for a repeat transit study following intervention. In terms of clinical significance, the results suggest that at 48hrs, in the real treatment group, the mean centre of radioactivity moves from the transverse colon to the lower descending colon (3.48 vs. 4.28).

It is a widely held belief that constipation and soiling are associated with obesity [311]. However, in the current study, 27 of the 35 children (77%) were either healthy or underweight. In 1995, the proportion of overweight or obese children and adolescents aged 2-17 years was 21% for boys and 23% for girls [312] and it is believed that in the last 10 years these figures have further increased. This shows that our study population is entirely representative of the Australian population as a whole and that STC is not associated with obesity.

Many of the children in the trial reported an increase in rectal sensation, following treatment with IFT, in association with an increase in their ability to hold back defecation and discriminate between formed, loose or gaseous stools. The anal canal is innervated both by free nerve ending and sensory organs with the maximum density of nerve endings being in the region of the anal crypts and the adjacent proximal mucosa (the 'transition zone') [313]. Distal to this region the anal mucosa is sensitive to pain, temperature and touch whilst the proximal rectal mucosa is not sensitive to pain but instead is sensitive to pressure changes due to the existence of numerous Golgi-Mazzoni bodies and pacinian corpuscles [314]. Since the rectum is not sensitive to pain, but is sensitive to distension of its lumen, it has been hypothesised that the sensation of rectal fullness is not a result of mucosal stimulation but instead arises from stimulation of the pelvic floor muscles and receptors in surrounding structures [313]. However, the precise role of anorectal sensation in the maintenance of continence is unclear.

The 'anal sampling reflex' consists of opening of the upper anal canal following rectal filling so that the rectal contents can come into contact with the sensate anal mucosa. It is seen in normal subjects up to 7 times an hour and is thought to aid in distinction between flatus and liquid or solid stool [314]. Despite its perceived importance, its frequent loss following ileoanal or coloanal anastomosis does not, for the most part, appear to result in faecal incontinence [315]. In addition, replication of loss of the sampling reflex, by applying lignocaine gel into the rectum of healthy subjects, does not result in incontinence of instilled liquid [316].

A study in 1984 in which Loening-Bauke assessed anorectal function (by means of anorectal manometry) in healthy children and in children with constipation (both with and without soiling), revealed that children with constipation (regardless of soiling state) had a lower anal resting tone and pull through pressure than the healthy controls. This abnormal rectal function was still apparent when the investigation was repeated up to 4 years after apparently successful treatment [317]. However, despite these findings, the subjects in the current study appear to have an improvement in their rectal perception and function.

The concept of applying electrical stimulation to improve faecal continence is not a new one however to date most techniques have employed trans-anal application, or direct implantation, of devices. There have been mixed reports regarding the efficacy of anal sphincteric electrical stimulation by means of an anal canal electrode [318-320]. It is thought that application of a tetanising stimulus to the anal sphincter and pelvic floor, resulting in contraction of the anal musculature, over time builds up and improves sphincter tone and contractility.

Greater success has been reported with sacral nerve stimulation (SNS). Like interferential therapy, the primary application of SNS was for the treatment of urinary incontinence [321-323]. Since this time, several studies have been performed that have assessed its efficacy in subjects with constipation and/or faecal incontinence; the use of SNS is advocated in subjects who have an intact anal sphincter and nervous system but who have a functional mechanical deficit [203-205 324-326]. Although, as with all electrotherapy, the precise mechanism of action of SNS remains

unknown, it is believed to work via neuromodulation. In general, peripherally applied electric current is thought to exert an influence centrally by altering the balance between excitation and inhibitory neural control resulting in a change in the neural drive [171]. It is likely that these changes are mediated by supraspinal as well as spinal pathways [327]. A number of physiological changes have been noted following electrical stimulation including an increase in afferent C fibre activity, an increase in the release of neurotransmitter substances (in the bladder), an increase in beta adrenergic activity, a reduction in cholinergic activity and changes in VIP and serotonin (smooth muscle relaxants) concentration [328]. Electric current has also been shown to stimulate the release of endorphins and encephalins in cerebral spinal fluid [328].

SNS involves applying a low amplitude electrical stimulation directly to a sacral nerve via an electrode inserted through the corresponding sacral foramen. Most benefit appears to be gained through stimulation of the third sacral nerve root (S3), a mixed nerve containing voluntary somatic, afferent sensory and efferent autonomic motor nerves [329]. Although the means by which sub-sensory stimulation produces the clinical results is unknown, direct stimulation of S3 produces elevation of the pelvic floor through external sphincter and levator contraction along with plantar flexion of the great toe [314]. SNS is achieved through the implantation of either temporary or permanent stimulating devices; permanent electrodes are now able to be inserted using a minimally invasive percutaneous technique with the stimulator placed in a pocket below the superficial fascia in the buttock [329].

Several studies have evaluated the efficacy of SNS either for the treatment of faecal incontinence [179 330] or constipation [324 326]. The studies concluded that SNS can lead to significant improvement in selected patients with faecal incontinence characterised by a reduction in episodes of faecal incontinence along with an improvement in ability to defer defecation. Although a period of temporary stimulation is able to determine in most instances those who will benefit from SNS, the studies found that despite having met the criteria for permanent device insertion, not all patients then go on to experience an improvement in their symptoms. In terms of treating patients with constipation, the studies found that SNS had the ability to increase their number of bowel movements and, as with the current study, reduce their abdominal pain and bloating. Dinning et al showed that although SNS had the capacity to induce pan-colonic propagating sequences as recorded by intraluminal colonic manometry, the stimulation parameters necessary to optimise colonic response remain unclear [324]. Stimulation of the S3 nerve root significantly enhanced antegrade colonic activity however stimulation of the S2 nerve root increased retrograde activity. They also experimented with different stimulus frequency and found that depending on the precise application of stimulators and pacing devices the optimum frequency could vary widely. They concluded that additional formal evaluation of frequencies and pulse width is required in order to determine the best possible treatment parameters.

The most apparent advantage of IFT over SNS is its non-invasive nature that subsequently makes it an attractive treatment option in children. As previously discussed, investigation into the application of SNS has been progressing for many years with investigators still experimenting to determine optimum stimulus

parameters. The current study used IFT treatment parameters based on a pilot study that in turn was based upon current settings used in adult subjects to promote bladder stability [170]. IFT employs 4 electrodes (2 abdominal, 2 paraspinal) and the paraspinal electrodes are currently placed at a level midway between T9 and L2 vertebrae. Since SNS studies have demonstrated that S3 stimulation produces an increase in colonic antegrade propagating activity, it may well be that results can be further improved by changing the electrode placement. There is also some anecdotal evidence that abdominal stimulation may have a slowing effect on gastrointestinal motility, hence the traditional cure of massaging the abdomen to ease a stomach ache. It may be that paraspinal stimulation alone is suffice to produce the desired clinical effects. In the same way, it might well be that the form of electrical stimulation currently being employed is not optimal. Further research needs to be performed to clarify optimal electrode placement, current frequency and intensity and the type of electrical stimulation.

As previously stated, IFT is a painless well tolerated treatment modality. None of the subjects participating in the trial experienced any adverse effects related to their IFT nor did they request to leave the trial at any point due to dislike of treatment. Since the commencement of the trial, new IFT machines have been released onto the open market that are battery operated (cf. mains electricity) and are of a portable nature. Rather than having to visit a physiotherapist for treatment and having to remain completely stationary for the duration of the treatment period, subjects can now partake in quiet activities and walk around whilst receiving their treatment. This means that IFT is now much more accessible and will appeal to a wider group

of patients. The investigators who carried out the pilot study in 2003 investigating the use of IFT in children with STC arbitrarily chose 3 x 20 minute treatment sessions per week. Since an improvement in symptoms was demonstrated with this regimen, it was carried forward to this larger trial. As with the current parameters, it remains unclear as to whether or not this represents the optimal treatment frequency. With the advent of portable machines it may be easier to trial different, including more frequent, treatment regimes.

This study suffers from its relatively short time scale and small numbers. It will therefore be important to determine the long-term effects of stimulation and whether or not the small decrease in soiling and abdominal pain are maintained or deteriorate over time. This is especially important as previous studies suggest that placebo effects are usually short-lived rather than producing long-standing results. Similarly, it is unclear whether or not the decrease in colonic transit time suggested by the repeat nuclear transit studies will be sustained over time. This may be a harder question to answer owing to the considerable time required for each transit study and the poor compliance in attendance of study participants. Whether or not a different response would be evident with increased participant numbers also remains unknown. Slow transit constipation represents a specific form of chronic constipation and as such there is a relatively small available patient pool from which to recruit subjects. Although all participants have demonstrable colonic delay on nuclear transit studies they are likely to represent a heterogeneous group of pathologies and as such grouping them together to assess response is not ideal.

In conclusion, this study is the first to attempt to evaluate transcutaneous electrical stimulation compared to placebo stimulation in the management of children with chronic slow transit constipation. Although the results are disappointing, with only small perceivable clinical benefits, objective evidence suggest that there is a decrease in colonic transit time following treatment with interferential therapy. Much still remains unknown regarding optimal treatment regimens and clearly further research is required in order to ascertain its potential clinical effectiveness.

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8. Evaluation of colonic function in children with slow transit constipation and appendix stomas following the application of transcutaneous electrical stimulation

8. Evaluation of colonic function in children with slow transit constipation and appendix stomas following the application of transcutaneous electrical stimulation

8.1 Introduction

A small proportion of children with chronic slow transit constipation are unable to maintain a sociably acceptable level of continence by the usage of laxatives alone and require the formation of an appendix stoma. It is via this appendiceal conduit that regular antegrade enemas can be performed in order to keep the colon empty of faecal matter in an attempt to avoid faecal leakage and soiling [125].

This subset of children with STC also underwent therapy with interferential electrical stimulation as described in the previous chapter, however, in addition to the aforementioned measurements, the subjects also had 24 hour colonic manometry performed via their appendicostomy [76] both before and after intervention.

Colonic manometry is a means of examining pan-colonic motility. A pressure recording catheter is placed in the colon by either a retrograde (via colonoscopy) or antegrade (via oral ingestion or an appendicostomy) route [76]. This catheter is able to determine changes in intraluminal pressure which result from colonic motor activity. Eight-sixteen recording sites are spaced at 7.5-10 cm intervals along the catheter, beginning at 7.5cm from the catheter tip. The pressure signals from each site are then amplified and digitised to produce an interpretable readout on a computer screen.

Previous studies have shown that colonic activity occurs in propagating waves or sequences and that these can be in either an antegrade (antegrade propagating sequence - APS) or retrograde (retrograde propagating sequence - RPS) direction [155]. Pressure waves are defined as a predominantly monophasic pressure elevations of >5mmHg that have a discernable onset, peak and offset and that do not have features of strain artefact (strain is discernable as it produces simultaneous, often identical, pressure elevations at all recording sites). Propagating sequences are in turn defined as a collection of 3 or more pressure waves occurring at adjacent recording sites and having a conduction velocity of 0.2-12cm/sec [155]. High amplitude colonic propagating sequences have also been demonstrated and are associated with mass colonic movements such as defecation or the post-prandial gastro-colic reflex. In order for a propagating sequence to be described as high amplitude, the pressure at (at least) one of the recording sites must be equal to or greater than 116mmHg [155]. High pressure waves can also occur in an antegrade (high amplitude antegrade propagating sequence - HAAPS) or retrograde (high amplitude retrograde propagating sequence - HARPS) direction [76].

Although colonic motor patterns in children are poorly described, previous investigators have demonstrated that children with STC appear to have decreased antegrade propagating motor activity with an altered ratio between antegrade and retrograde pressure waves. They also lack normal colonic motor responses to waking and meal ingestion [76].

8.2 Hypothesis and aims

This study hypothesises that transcutaneous electrical stimulation (in the form of interferential therapy (IFT)) can increase bowel activity, and improve symptoms. The study aims to determine whether or not transcutaneous IFT can affect the symptoms of STC in children (frequency of defecation, soiling, and abdominal pain) and their colonic activity (as measured by colonic manometry).

8.3 Subjects and methods

8.3.1 Participants

The participant inclusion and exclusion criteria were the same as those described in chapter 7 with the following additional points:

- Participant had to have an existing appendix stoma that was placed at least 6 months previously and had not recently been revised or had recurrent problems with infection/severe over-granulation.
- The stoma did not have to currently be in use for the provision of antegrade continence enemas.
- Participant must have been willing, with no parental coercion, to participate in 2 rounds of colonic manometry and fully understand what the investigation entailed.
- Any subject who had previously had colonic manometry and was unable to tolerate the procedure was excluded.

8.3.2 Recruitment and intervention

Complete recruitment strategies and intervention are described in full in chapter 7.

8.3.3 Outcome measures

8.3.3.1 Primary outcome measure

The primary outcome measure is colonic activity as measured by colonic manometry. This includes frequency, amplitude, velocity and distance of propagation, site of origin and regional linkage of propagating sequences (antegrade and retrograde). Waking and postprandial responses are also assessed. The methods are described later in the chapter.

8.3.3.2 Secondary outcome measures

The secondary outcome measures are the bowel diary measurements outlined in Chapter 7 (including the primary outcome measure - this time recorded as a secondary outcome measure).

8.3.4 Timing of manometry

Children willing to participate were required to have 2 separate manometric recordings - one before and one after receiving IFT. The baseline recording had to have been performed any time before their first treatment, with no minimum time period specified. Some children had undergone colonic manometry as part of a previous study and this information was utilised to determine their baseline colonic motor function. Other children had both their studies performed as part of this study.

The second study was performed 8 weeks after completing a course of treatment with IFT.

8.3.5 Colonic manometry methods

Children participating were required to attend the Royal Children's Hospital for 3 consecutive days (Wednesday, Thursday and Friday). If they lived locally then they were given the option of returning home for the night on Wednesday, however if they lived a long way away, or were reluctant to go home, then they either spent the Wednesday night in the hospital's Medihotel or were admitted a day early as an inpatient to a ward. All participants spent the Thursday and Friday as inpatients. Participants were able to have a family member stay with them at all times. Prior to attending they were sent a letter (Appendix 21) outlining their admission details and containing instructions about how they should alter their washouts in the days leading up to the manometry. They were asked to cease all use of stimulant washout media (i.e. Bisacodyl, Phosphate/Dulcolax enemas) for the 5 days before coming in and to perform washout with water only on the Sunday and Tuesday.

The manometry catheter utilised was a custom-designed, 3.5mm (external diameter) balloon tipped 9-lumen (8-channel) extruded silicone catheter (Dentsleeve, Adelaide, South Australia, Australia) (Figure 21). The 8 recording side holes are spaced at 7.5cm intervals beginning 7.5cm from the tip of the catheter. The total length of the catheter is 180cm. The central lumen inflates a 5ml Foley-type balloon situated 2cm proximally from the tip of the catheter. The centre of the catheter is coated with barium sulphate in order to facilitate fluoroscopic visualisation.

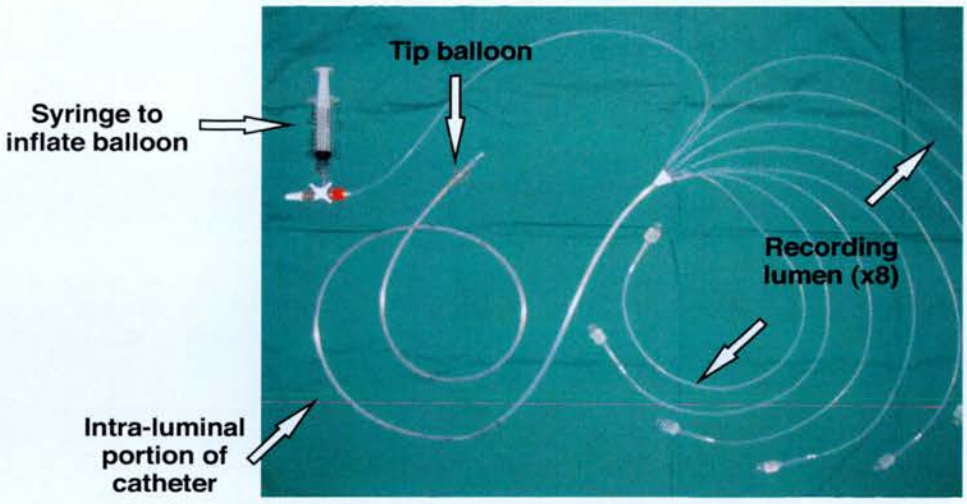


Figure 21 - *Colonic manometric recording catheter.*

The recording lumen were continuously perfused with degassed distilled water (Figure 53). The water is driven by a low compliance pneumohydraulic perfusion pump at a rate of 0.25ml/minute (Neomedix Systems Pty Ltd., Warriewood, New South Wales, Australia). The 8 lumens are connected to 8 external pressure transducers. The signals are amplified and digitised at 16Hz by preamplifiers using Polygram data acquisition software (Medtronic Australasia, Gladesville, New South Wales, Australia).

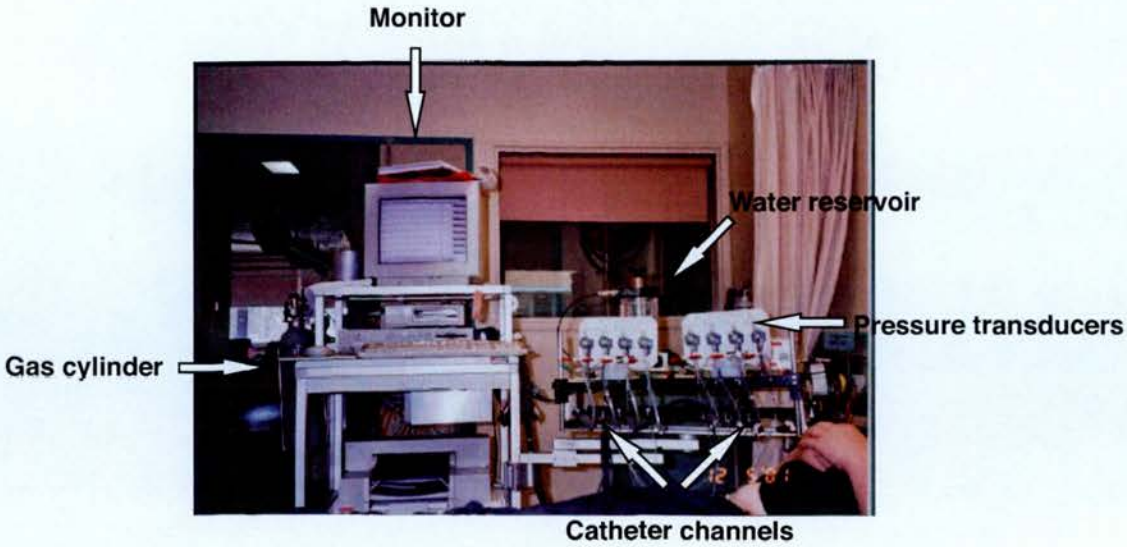


Figure 22 - *Manometry recording equipment.*

Day 1 (Wednesday) - Catheter insertion

Children and their parent(s) were asked to attend the Royal Children's Hospital at 9AM. They were met by MC and the specialist gastrointestinal nurse (DS) and taken to a treatment room in the gastrointestinal department. The procedure was explained once more and if the participant was happy to proceed they were asked to lie on an examination couch.

Having examined the appendicostomy site for any infection it was cleaned with alcohol (70%) swabs and both the stoma and peristomal skin were liberally coated with 1% lignocaine gel. After waiting an appropriate time for the lignocaine to become effective, any existing device within the appendicostomy was removed (i.e. chait button [128] or foley catheter). A 10Fr cut-off feeding tube was then passed into the appendicostomy and up to 5mg (5ml) of Bisacodyl (5mg/10ml pre-made solution, Rhone-Poulenc, Baulkham Hills, New South Wales, Australia) was

instilled. Bisacodyl has been shown to stimulate colonic contraction, by an unknown mechanism, and is used to aid propulsion of the manometry catheter around the colon (recording was commenced approximately 24hrs after the use of Bisacodyl to minimise any possible residual effects) [107]. The catheter was then lubricated and inserted into the appendicostomy (Figure 23). The balloon was inflated with 3ml water (to further aid antegrade propulsion) and the catheter was slowly advanced. Once all 8 side holes had been inserted, with the final hole within the caecum, the catheter was temporarily taped into position and the child was taken to fluoroscopy.

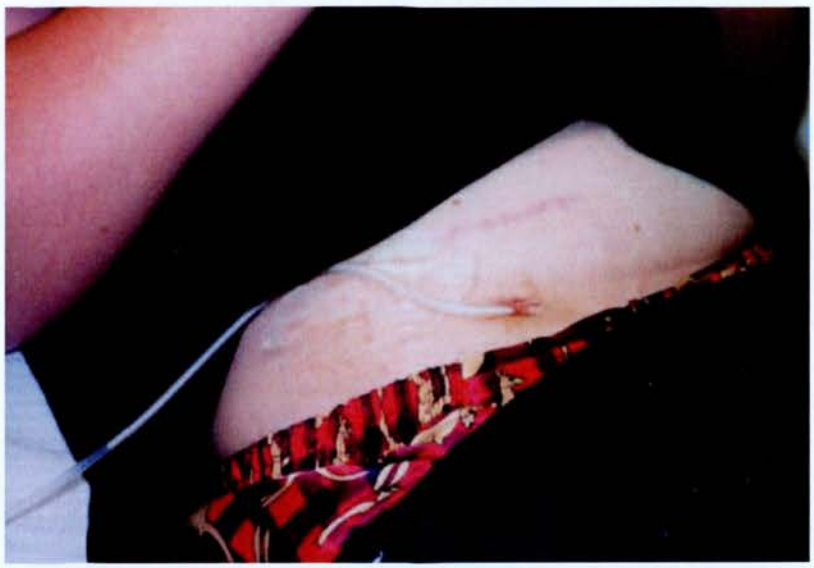


Figure 23 - *Appendicostomy with manometry catheter in place.*

In fluoroscopy, the child's abdomen was briefly screened and the exact position of the catheter determined. If the catheter was seen to be looped back on itself (Figure 24) it was withdrawn and readvanced, then the screening was repeated. Once a satisfactory position was obtained (Figure 25), the catheter was firmly secured with Hyperfix hypoallergenic tape, the balloon was deflated, and the child was free for the rest of the day. If the catheter was unable to be advanced without curling, then

the appropriate length of catheter was again inserted and the catheter was secured. The child was encouraged to walk around and eat normally for the next few hours, in an attempt to encourage the colon to advance the catheter, before returning to fluoroscopy for repeat screening. As previously stated, once the catheter was in a satisfactory position it was taped and the child was free for the remainder of the day. If an acceptable position was unattainable then further screening was performed on the Thursday morning before commencing manometric recording.

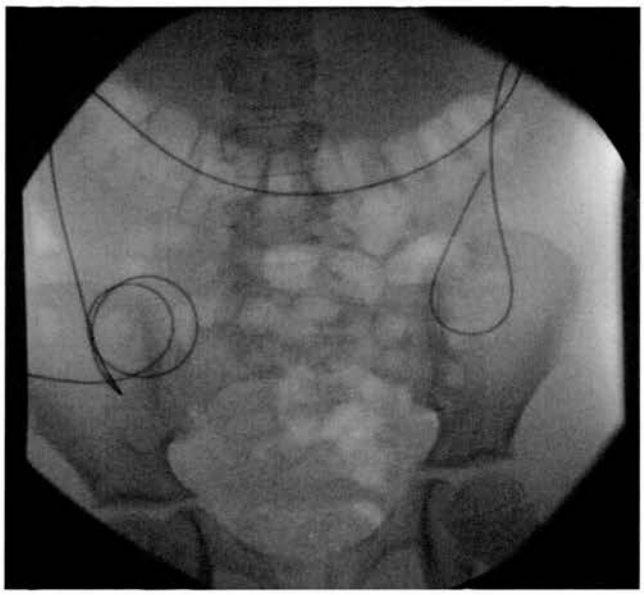


Figure 24 - *Fluoroscopy screening demonstrating looping of tip of manometry catheter in descending colon.*

Day 2 - Commencement of manometric recording

The child was either asked to attend the fluoroscopy suite at 8AM for repeat screening, or, if the catheter position had already been deemed satisfactory, they were asked to report to the surgical ward after breakfast (approx 9AM). The skin

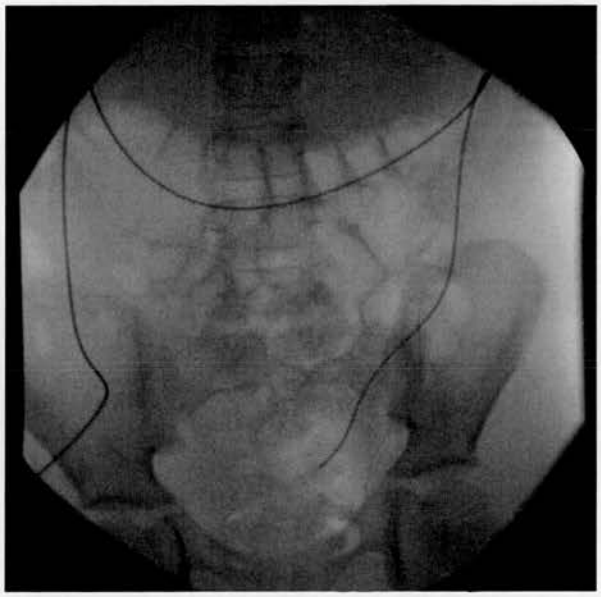


Figure 25 - *Fluoroscopy screening demonstrating correct positioning of manometry catheter (side hole 1 in rectum, side hole 8 in caecum).*

integrity around the appendicostomy site was checked and the child settled into their bed. As they had to remain recumbent or semi-recumbent for the next 24hrs they were reminded that they would have to use a bedpan or bottle for toileting and it was ensured that they had plenty of activities to occupy their time.

As calorie intake, along with the protein:carbohydrate:fat ratios in a meal, has been shown to affect colonic motility, participants were provided with a special menu (Appendix 22) with each menu choice consisting of 17% protein, 34% carbohydrate and 45% fat. The calorific content of each meal was also standardised: breakfast 300kCal (1255kJ), lunch 1000kCal (4184kJ) and dinner 1000kCal (4184kJ). The participants were discouraged from ingesting any other food or drink during the recording period apart from water if absolutely necessary.

Having attached the catheter to the perfusion channels and having ensured that each recording site is active, recording was commenced and continued for an uninterrupted 24hr period. During the study, participants were asked to complete an event diary documenting all their activities such as eating, postural changes, sleeping/waking, micturition/defecation, abdominal sensations and passage of flatus (Appendix 23). Diary events were subsequently correlated with manometric data during analysis of the recordings.

Regular checks were made throughout the 24hr period to ensure that the machine was recording correctly and that the participant was not experiencing any discomfort.

Day 3 - IFT session and catheter removal

After 24hrs the recording was complete. The final position of the manometry catheter was checked with a plain abdominal film (this was also used to calculate the relative positions of the recording side holes within the colon) (Appendix 24). The appendicostomy site and catheter were once again lubricated with 1% lignocaine gel and the catheter was slowly withdrawn until it was removed. If the child had an existing device within their appendicostomy then a new one was replaced appropriately.

8.3.6 Data analysis

Analysis of the recordings was performed visually with propagating sequences (antegrade and retrograde) and high amplitude propagating sequences (antegrade and retrograde) identified using the criteria previously defined (see Introduction) [155]. Analysis was performed in a manner identical to that formerly described by Bampton et al [155]. Regional baselines were established, meaningful activity identified visually, then the amplitude and velocity calculated with computer assistance. Data were then entered into Excel and further analysis performed. For antegrade and retrograde activity, the frequency, amplitude and distance of propagation were compared before and after IFT using paired *t* tests. Data were also examined to determine whether or not the propagating sequences were linked to each other. Propagating sequences were defined as linked if they were in the same direction with different originating side holes but overlapping side hole activity. The frequency of events was expressed in terms of 24 separate hourly periods. All data are expressed as mean (± SEM) unless otherwise indicated. Recordings were also examined for possible waking and post-prandial responses, defined as an increase in activity for the hour following the event (recorded in the patient diary). All p values < 0.05 were considered as statistically significant.

Bowel diary and QoL data were analysed as previously described in Chapter 7.

8.4 Results

Six children underwent colonic manometry pre- and post-treatment with IFT (12 studies). Their demographics are shown below. Complete data were available for

analysis on 5 of the subjects due to a technical error that resulted in 8 hours of irretrievable post-IFT data for one subject (subject 6). This meant that paired analysis (pre- and post-IFT) could not be performed for this subject.

Table 31 - *Demographics of study population.*

Number of children	6
Male:Female	5:1
Average age (yrs)	13.4
Male/Female (yrs)	13.8/11.8
Age range (yrs)	9.2-19
Average duration of symptoms (yrs)	12.6
Range of duration of symptoms (yrs)	6.2-19.0
Symptoms since birth	4/6
Abdominal pain	2/6
Average score /10	4.5
Soiling	5/6
Severe (daily/constant) soiling	2/5
Appendicostomy	6/6
Weight	
Underweight (BMI <5th centile)	0/6
Healthy (BMI 5-85th centile)	3/6
Overweight (BMI 85-95th centile)	0/6
Obese (BMI >95th centile)	3/6
Medication	6/6

The catheter tip was located in the lower descending colon or sigmoid colon in 9 of the 12 studies. In two subjects, despite having all side holes present within the colon, the catheter only reached the splenic flexure. All subjects tolerated the procedure well and did not request the catheter to be removed.

8.4.1 Colonic activity

The colonic activity for each subject (antegrade and retrograde activity and high amplitude activity) is shown in tables 32-35. Data for subject 6 are incomplete as they lack 8hours of recorded material.

Table 32 - *Frequency and properties of antegrade colonic activity.*

Subject	Pre/Post IFT	All antegrade propagating sequences (APS)				
		Number of APS	Side hole of origin (mode)	Distance travelled/ number of holes (mode)	Duration/ sec (mean)	Velocity/ m/sec (mean)
Subject 1	Pre	26	2	4	40	0.83
	Post	93	4	3	15.4	2.15
Subject 2	Pre	1	1	8	11	4.77
	Post	128	6	3	15.2	2.01
Subject 3	Pre	31	5	3	26.4	1.70
	Post	57	1	3	25.8	1.18
Subject 4	Pre	61	6	3	16	1.66
	Post	155	6	3	23.2	1.41
Subject 5	Pre	128	5	3	13.6	2.35
	Post	140	1	3	21.7	1.67
Subject 6	Pre	60	1	3	17.9	1.82
	Post *	24	1	3	27.1	1.40

Table 33 - *Frequency and properties of high amplitude antegrade colonic activity.*

Subject	Pre/Post IFT	High amplitude antegrade propagating sequences (HAAPS)				
		Number of HAAPS	Side hole of origin (mode)	Distance travelled/ number of holes (mode)	Duration/ sec (mean)	Velocity/ m/sec (mean)
Subject 1	Pre	13	5	4	33.9	0.96
	Post	18	6	3	35.7	1.05
Subject 2	Pre	0				
	Post	14	1	5	26.4	2.68
Subject 3	Pre	10	1	7	45.8	0.60
	Post	15	1	4	39.8	0.89
Subject 4	Pre	1	3	6	32.0	1.17
	Post	7	1	8	49.6	1.27
Subject 5	Pre	0				
	Post	0				
Subject 6	Pre	7	5	4	34.0	0.77
	Post *	4	5	3	34.0	0.73

Table 34 - *Frequency and properties of retrograde colonic activity.*

Subject	Pre/Post IFT	All retrograde propagating sequences (RPS)				
		Number of RPS	Side hole of origin (mode)	Distance travelled/ number of holes (mode)	Duration/ sec (mean)	Velocity/ m/sec (mean)
Subject 1	Pre	0				
	Post	20	8	3	6.7	2.81
Subject 2	Pre	4	6	6	25.3	2.08
	Post	37	8	3	16.9	1.31
Subject 3	Pre	7	8	3	11.1	2.40
	Post	14	8	3	12.6	1.66

Subject 4	Pre	53	4	3	12.8	1.98
	Post	78	8	3	17.2	1.53
Subject 5	Pre	134	3	3	14.9	1.57
	Post	384	5	3	11.9	1.97
Subject 6	Pre	77	8	3	7.6	2.85
	Post *	17	8	3	6.6	3.25

Table 35 - *Frequency and properties of high amplitude retrograde colonic activity.*

Subject	Pre/Post IFT	High amplitude retrograde propagating sequences (HARPS)				
		Number of HARPS	Side hole of origin (mode)	Distance travelled/ number of holes (mode)	Duration/ sec (mean)	Velocity/ m/sec (mean)
Subject 1	Pre	0				
	Post	0				
Subject 2	Pre	3	6	6	30.0	1.18
	Post	0				
Subject 3	Pre	0				
	Post	1	8	4	36.0	0.63
Subject 4	Pre	1	3	3	17.0	0.88
	Post	1	8	3	22.0	0.68
Subject 5	Pre	0				
	Post	0				
Subject 6	Pre	0				
	Post *	0				

8.4.1.1 Frequency of propagating sequences (PS)

Following treatment with IFT there was an increase in total colonic activity (mean 89 ± 47 vs. 221 ± 80; $p = 0.03$) (Figure 26). There was an increase in both antegrade

(mean 49 ± 22 vs. 115 ± 18; $p = 0.03$) and retrograde (mean 40 ± 25 vs. 107 ± 70; $p = 0.20$) activity (Figures 27 and 28).

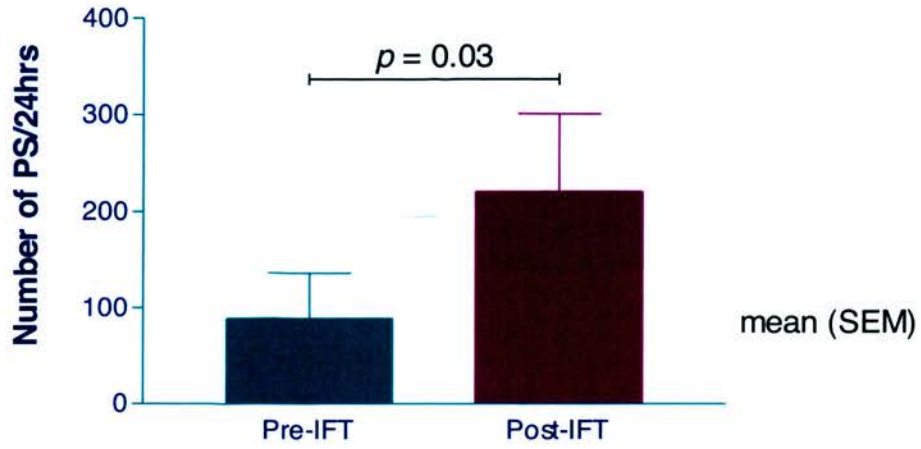


Figure 26 - *Total number PS, antegrade and retrograde, in each 24hr study, before and after treatment with IFT (paired t-test).*

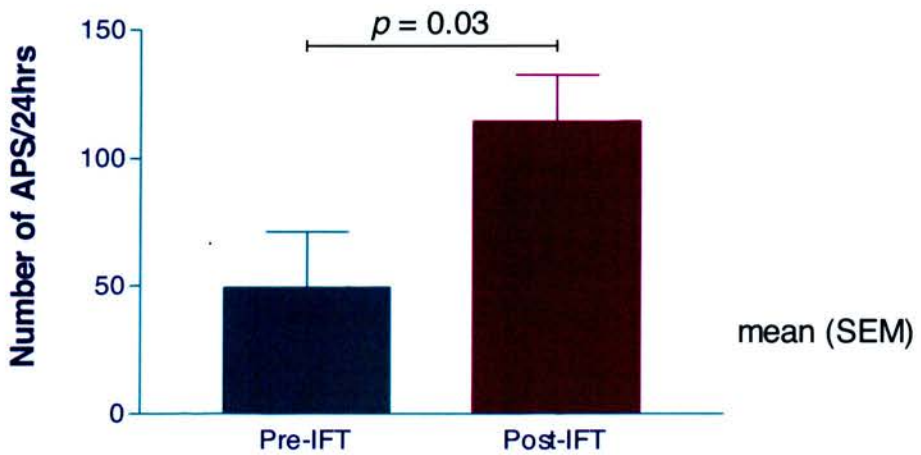


Figure 27 - *Number of antegrade propagating sequences (APS), in each 24hr study, before and after treatment with IFT (paired t-test).*

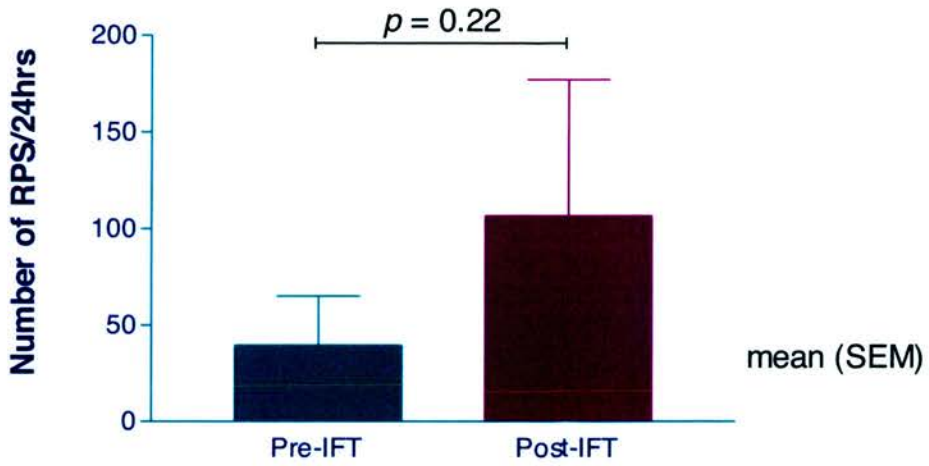


Figure 28 - *Total number of retrograde propagating sequences (RPS), in each 24hr study, before and after treatment with IFT (paired t-test).*

Although there was an increase in antegrade high amplitude propagating sequences (HAPS) (mean 5 ± 3 vs. 11 ± 3; $p = 0.06$), there was a decrease in high amplitude retrograde propagating activity (HARPS) (mean 0.8 ± 0.6 vs. 0.4 ± 0.2; $p = 0.59$).

8.4.1.2 Amplitude of propagating sequences

The mean amplitude of antegrade PS was 52 ± 10 mm Hg pre-treatment compared to 36 ± 4 mm Hg post-treatment ($p = 0.09$) and the mean amplitude of retrograde PS was 34 ± 9 mm Hg pre-treatment compared to 22 ± 1 mm Hg post-treatment ($p = 0.24$). With regards to HAPS, the mean amplitude prior to IFT was 98 ± 7 mm Hg compared to 90 ± 14 mm Hg after IFT ($p = 0.61$).

8.4.1.3 Velocity and propagation distance

There was no significant change in average velocity of either antegrade or retrograde propagating sequences following treatment with IFT (antegrade - 1.7 ± 0.2 cm/sec

vs. 1.6 ± 0.2 cm/sec; $p = 0.78$ and retrograde - 2.2 ± 0.2 cm/sec vs. 1.9 ± 0.3 cm/sec; $p = 0.43$). There was also no significant difference in HAPS velocity pre- and post-intervention (0.9 ± 0.1 cm/sec vs. 1.0 ± 0.1 cm/sec; $p = 0.20$).

There was no significant difference in the propagation distance when the average number of side holes travelled by each propagating sequence was compared pre- and post-intervention. This was so for antegrade (4.2 ± 0.2 vs. 4.5 ± 0.1; $p = 0.43$), retrograde (3.9 ± 0.6 vs. 3.4± 0.1; $p = 0.53$) and high amplitude antegrade (5.0 ± 0.3 vs. 5.8 ± 0.8; $p = 0.19$).

8.4.1.4 Site of origin of propagating sequences

Pre-treatment with IFT, the most common site of origin of antegrade PS was the caecum (R1) (mean ± SD of total activity = 35% ± 37%). The most common site of retrograde PS origin was the splenic flexure/descending colon (mean ± SD of total activity = 26% ± 20%) (Figure 29).

Post-treatment with IFT, the most common site of origin of antegrade PS was still the caecum (R1) (mean ± SD of total activity = 25% ± 13%). However, the most common site of retrograde PS origin had become the rectosigmoid (mean ± SD of total activity = 58% ± 30%) (Figure 30).

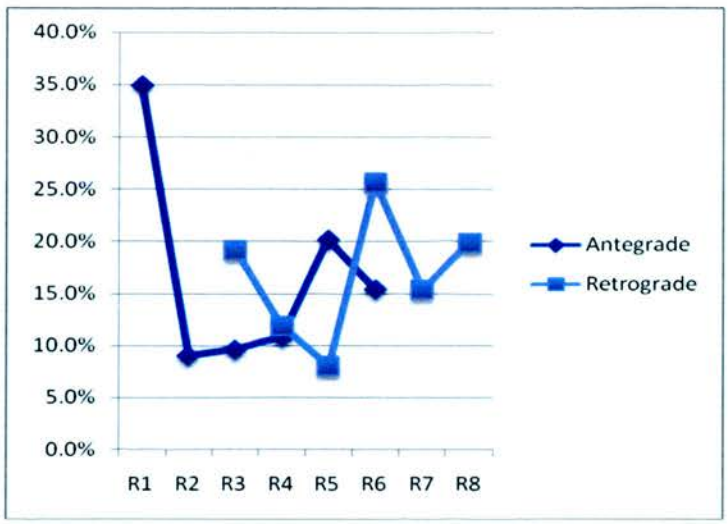


Figure 29 - *Distribution of site of origin (% total activity) for both antegrade and retrograde propagating sequences pre-treatment with IFT.*

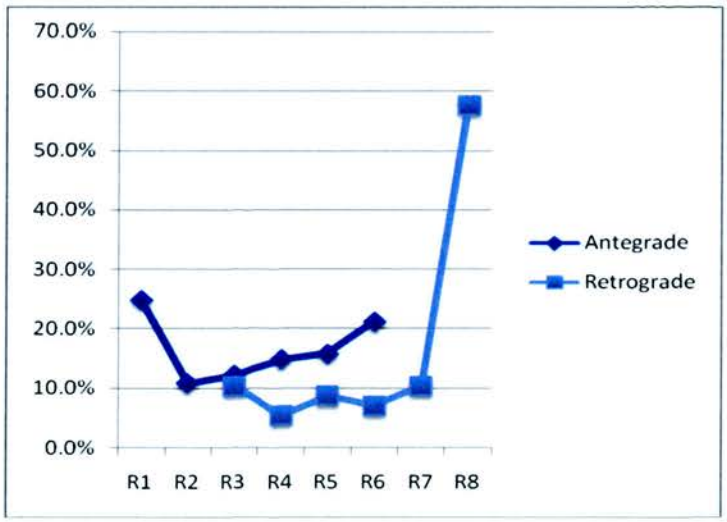


Figure 30 - *Distribution of site of origin (% total activity) for both antegrade and retrograde propagating sequences post-treatment with IFT.*

8.4.1.5 Regional linkage

As previously stated, sequential propagating sequences were defined as being *regionally linked* if they started at different side holes, were in the same direction and had overlapping side hole activity. In addition, if 3 or more regionally linked PS occurred sequentially, this was defined as a colonic complex. Pre treatment with IFT, 65% ± 13% (mean ± SD) of antegrade propagating sequences and 61% ± 10% (mean ± SD) of retrograde propagating sequences were linked (Figure 31).

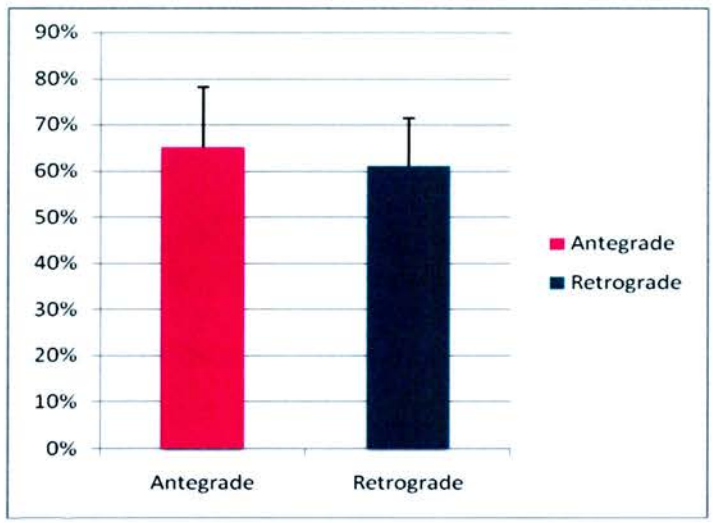


Figure 31 - *% of total colonic activity, antegrade and retrograde, that could be defined as being regionally linked pre-treatment with IFT.*

Post treatment with IFT, only 56% ± 10% (mean ± SD) of antegrade propagating sequences and 33% ± 23% (mean ± SD) of retrograde propagating sequences could be defined as being linked (Figure 32).

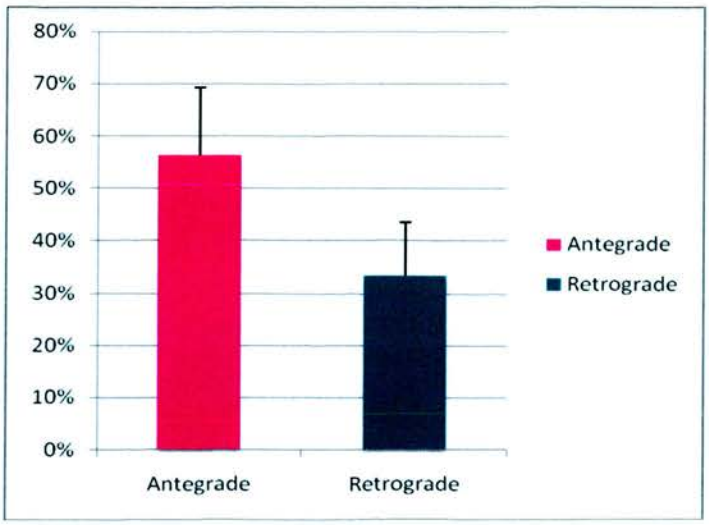


Figure 32 - *% of total colonic activity, antegrade and retrograde, that could be defined as being regionally linked post-treatment with IFT.*

When looking at the antegrade-linked activity, pre-treatment 4 of the 5 subjects had activity that formed colonic complexes whereas post-treatment all 5 subjects had colonic complexes (36% ± 8.5% vs. 44.5% ± 6.0% of total antegrade linked activity; $p = 0.18$). With regards to the retrograde linked activity, only 2 of the 5 subjects formed retrograde colonic complexes prior to intervention compared to 3 subjects following IFT (15.9% ± 12.5% vs. 26.4% ± 11.0% of total antegrade linked activity; $p = 0.35$).

8.4.1.6 Waking and postprandial responses

Recordings were examined for waking or postprandial responses identified by a high amplitude activity following waking or ingestion of foodstuffs (Figure 33). Times of meals obtained from the patient diary (Appendix 33) were correlated with manometric events.

Data were available for 4 subjects both pre and post intervention with interferential therapy. The results are shown in Table 36.

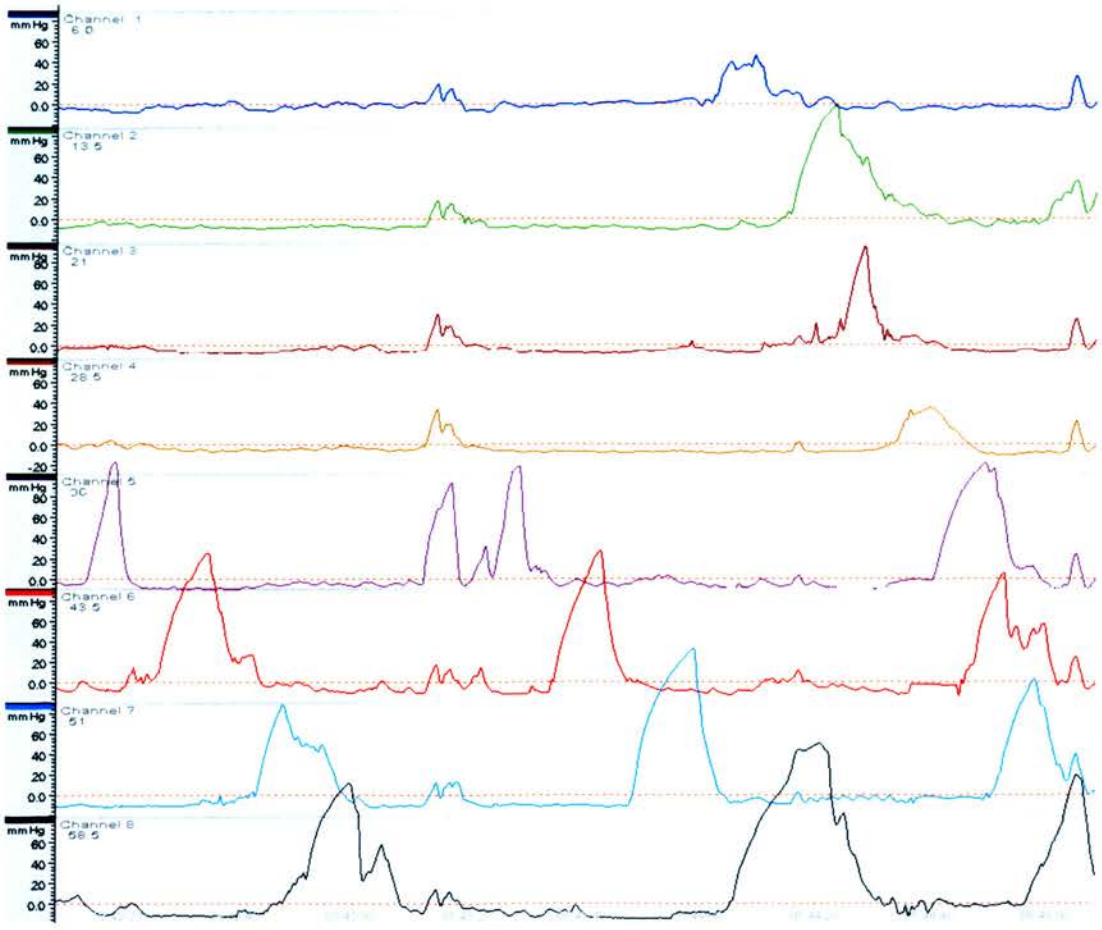


Figure 33 - *Manometric recording illustrating a post-prandial response.* *There are multiple high amplitude propagating sequences (HAPS) one originating from the splenic flexure (channel 5) and another in the caecum (channel 1).*

Table 36 - *Number of subjects with waking and post-prandial responses before and after intervention with IFT.*

		Post-prandial Response		
	Waking Response	Breakfast	Lunch	Dinner
Pre IFT	0/4	0/4	1/4	2/4
Post IFT	3/4	2/4	1/4	3/4

8.4.2 Bowel diary data

8.4.2.1 Defecation

8.4.2.1.1 Spontaneous defecation

The mean number of 'spont' defecation episodes per week for each 28 day treatment period for the manometry group are shown in table 37. All data sets demonstrated normal Gaussian distribution.

Table 37 - *Table showing episodes of 'spontaneous' defecation (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of 'spont' defecation /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	1.60	1.10
	Treatment (4 weeks)	0.95	1.24
	1st post treatment (4 weeks)	2.30	0.89
	2nd post treatment (4 weeks)	1.45	0.87

There was no statistical difference in the number of episodes of 'spont' defecation when comparing the pre-treatment with the treatment (mean 1.60 vs. 0.95; $p = 0.38$), first post-treatment (mean 1.60 vs. 2.30; $p = 0.35$) or second post-treatment (mean 1.60 vs. 1.45; $p = 0.82$) periods.

8.4.2.1.2 Sit defecation

The mean number of 'sit' defecation episodes per week for each 28 day treatment period for the manometry group are shown in table 38. All data sets demonstrated normal Gaussian distribution.

Table 38 - *Table showing episodes of 'sit' defecation (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of 'sit' defecation /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	2.00	1.36
	Treatment (4 weeks)	2.15	1.26
	1st post treatment (4 weeks)	2.25	1.57
	2nd post treatment (4 weeks)	1.85	1.61

There was no statistical difference in the number of episodes of 'sit' defecation when comparing the pre-treatment with the treatment (mean 2.00 vs. 2.15; $p = 0.70$), first post-treatment (mean 2.00 vs. 2.25; $p = 0.62$) or second post-treatment (mean 2.00 vs. 1.85; $p = 0.79$) periods.

8.4.2.1.3 Total defecation

The mean number of 'total' defecation episodes per week for each 28 day treatment period for the manometry group are shown in table 39. All data sets demonstrated normal Gaussian distribution.

Table 39 - *Table showing episodes of 'total' defecation (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of 'total' defecation /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	3.60	1.51
	Treatment (4 weeks)	3.10	0.14
	1st post treatment (4 weeks)	4.55	1.20
	2nd post treatment (4 weeks)	3.30	1.55

There was no statistical difference in the number of episodes of total defecation when comparing the pre-treatment with the treatment (mean 3.60 vs. 3.10; $p = 0.53$), first post-treatment (mean 3.60 vs. 4.55; $p = 0.28$) or second post-treatment (mean 3.60 vs. 3.30; $p = 0.74$) periods.

8.4.2.2 Soiling

9.3.2.2.1 Stain soiling

The mean number of 'stain' soiling episodes per week for each 28 day treatment period for the manometry group are shown in table 40. All data sets demonstrated normal Gaussian distribution.

Table 40 - *Table showing episodes of 'stain' soiling (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of 'stain' soiling /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	1.30	2.91
	Treatment (4 weeks)	0.50	0.87
	1st post treatment (4 weeks)	0.30	0.67
	2nd post treatment (4 weeks)	0.30	0.54

There was no statistical difference in the number of episodes of 'stain' soiling when comparing the pre-treatment with the treatment (mean 1.30 vs. 0.50; $p = 0.44$), first post-treatment (mean 1.30 vs. 0.30; $p = 0.37$) or second post-treatment (mean 1.30 vs. 0.30; $p = 0.40$) periods.

8.4.2.2.2 Scrape soiling

The mean number of 'scrape' soiling episodes per week for each 28 day treatment period for the manometry group are shown in table 41. All data sets demonstrated normal Gaussian distribution.

Table 41 - *Table showing episodes of 'scrape' soiling (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of 'scrape' soiling /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	0.75	1.68
	Treatment (4 weeks)	0.40	0.76
	1st post treatment (4 weeks)	0.85	1.76
	2nd post treatment (4 weeks)	0.60	1.34

There was no statistical difference in the number of episodes of 'scrape' soiling when comparing the pre-treatment with the treatment (mean 0.75 vs. 0.40; $p = 0.45$), first post-treatment (mean 0.75 vs. 0.85; $p = 0.18$) or second post-treatment (mean 0.75 vs. 0.60; $p = 0.37$) periods.

8.4.2.2.3 Total soiling

The mean number of 'total' soiling episodes per week for each 28 day treatment period for the manometry group are shown in table 42. All data sets demonstrated normal Gaussian distribution.

There was no statistical difference in the number of episodes of 'total' soiling when comparing the pre-treatment with the treatment (mean 1.40 vs. 0.85; $p = 0.50$), first post-treatment (mean 1.40 vs. 1.10; $p = 0.46$) or second post-treatment (mean 1.40 vs. 0.85; $p = 0.42$) periods.

Table 42 - *Table showing episodes of 'total' soiling (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of 'total' soiling /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	1.40	3.13
	Treatment (4 weeks)	0.85	1.51
	1st post treatment (4 weeks)	1.10	2.32
	2nd post treatment (4 weeks)	0.85	1.76

8.4.2.3 Abdominal pain

The mean number of episodes of abdominal pain per week for each 28 day treatment period for the manometry group are shown in table 43. All data sets demonstrated normal Gaussian distribution.

Table 43 - *Table showing episodes of abdominal pain (mean + SD) pre- and post- intervention.*

Manometry group	Treatment period	Number of episodes of abdominal pain /week	
		Mean	SD
SUBJECTS (n=5)	Pre-treatment (4 weeks)	0.60	0.84
	Treatment (4 weeks)	0.15	0.13
	1st post treatment (4 weeks)	0.45	0.67
	2nd post treatment (4 weeks)	0.45	0.67

There was no statistical difference in the number of episodes of abdominal pain when comparing the pre-treatment with the treatment (mean 0.60 vs. 0.15; $p = 0.26$), first post-treatment (mean 0.60 vs. 0.45; $p = 0.21$) or second post-treatment (mean 0.60 vs. 0.45; $p = 0.77$) periods.

8.5 Discussion

Colonic manometry is slowly becoming recognised not only as a research tool but also as a clinical diagnostic measure for assessing colonic motor function. However, most centres still only perform short, 4 hour, recordings with colonoscopically placed recording catheters [5 77 158]. It is only recently that the technique of antegrade catheter placing via an appendicostomy has been described in children that requires no sedation and enables longer recording times [76]. By employing this technique, this study was able to compare 24 hour colonic manometric activity before and after intervention with interferential therapy. One of the advantages of 24-hour recording is that it allows satisfactory assessment of waking and post-prandial responses as well as providing sufficient length of recording in order to adequately ascertain the presence or absence of high amplitude activity. Unfortunately, in order to obtain the manometric recordings the subjects have to remain in bed for 24 hours, in a recumbent or semi-recumbent position, which may decrease the amount of observed colonic activity. However, since in this study both recordings were obtained using an identical protocol, the results and subsequent conclusions should not be affected. Other advantages of this method of insertion compared to colonoscopic placement is that it does not require a prepared colon and that it provides recording from the whole colon rather than just the distal portion [76].

This study found that total colonic activity increased following intervention with IFT ($p = 0.03$). This was, however, only so for antegrade activity ($p = 0.03$) and not so for retrograde activity ($p = 0.22$). Although, there was an increase in high amplitude antegrade propagating sequences following electrical it did not reach statistical significance ($p = 0.06$). Although the mechanism by which transcutaneous electrical stimulation could perhaps influence colonic motor activity remains unclear, the reactivity of the colon appears to increase with a small but consistent increase in antegrade colonic activity. Potential theories include increased activity of the colonic pacemaker interstitial cells of Cajal (ICC) or changes in the balance of excitatory and inhibitory neuronal transmission [20]. The latter possibly occurring secondary to alterations in neurotransmitter release, or augmented nerve fibre activity, or by an as yet completely unidentified mechanism.

Although some centres diagnose subjects with STC based on the apparent absence of high amplitude activity [77 158], previous 24-hour studies have shown that our cohort with proven STC on nuclear scintigraphy do in fact have the capacity to generate high amplitude activity although there is a reduction in the frequency of such events [76]. The current study showed that there was a small, and nearly significant ($p = 0.06$), increase in the number of HAPS observed in each 24-hour study period following intervention with IFT. Normal data from controls predict that there should be 8.5-11.5 HAPS per 24-hour period [155]; the mean number of events per 24-hours increased from 5 pre-IFT to 11 following IFT showing that the majority of children are experiencing, or at least approaching, normality in terms of expected HAPS frequency. HAPS are often the result of colonic physiological reactions such as

waking or post-prandial responses. Following electrical stimulation there appeared to be an increase in these physiological responses - both following waking and eating. Early morning increases in activity can be difficult to differentiate between post-waking and post-breakfast responses; however 3 of the 4 subjects also experienced an increase in HAPS following their evening meal suggesting that they did have the ability to generate a true post-prandial response.

Despite having a small increase in antegrade colonic motor activity after IFT, there was no change in amplitude, velocity or propagating distance. If anything, there was a trend towards a decrease in amplitude with regard to both antegrade and retrograde activity. Although it would be reasonable to assume that a decrease in amplitude of antegrade activity would affect the efficacy of forward propulsive movement of faecal matter, it may well be that any effect is in part counteracted by the increase in total number of antegrade propagating sequences. It has previously been demonstrated that low amplitude sequences are in fact able to produce propulsive movement of intestinal contents [324]. Little is known about the function of retrograde propagating sequences but they are present in healthy control subjects with an approximate ratio of antegrade:retrograde activity of 3:1 [155]. As such, nothing can be concluded from a decrease in the amplitude of retrograde activity since it is unclear whether or not this is deleterious or in fact advantageous.

There was no significant change in velocity of antegrade, retrograde or high amplitude propagating sequences when comparing pre- and post- intervention values (see section 8.4.1.3). Previous studies have highlighted that the mean velocity of

HAPS in normal subjects is considerably slower than the mean conduction velocity of non-high amplitude antegrade activity [155]. Pre-electrical therapy recordings in the current study population supported these findings (0.9 ± 0.1 cm/sec vs. 1.7 ± 0.2 cm/sec; $p = 0.03$) and the difference was unaffected by IFT.

There was no alteration in the mean propagating distance of antegrade, retrograde or high amplitude antegrade propagating sequences after electrical therapy (see section 8.4.1.3). It has been well documented that in healthy controls high amplitude propagating sequences propagate further than lower amplitude sequences [155]. Again, pre-intervention data for the study subjects supported these findings (5.0 ± 0.3 vs. 4.2 ± 0.2; $p = 0.06$) and this difference remained unaltered following electrical stimulation.

Prior to treatment with IFT, the majority (34.9%) of antegrade propagating sequences originated in the caecum. Although following intervention the commonest site of origin remained the caecum (24.9%), the distribution was more evenly spread along the colon. Previous studies in normal subjects have shown that antegrade propagating sequences arise more frequently in the caecum than in any other region [155]. It has recently been proposed that it may be favourable to exhibit local regional variation in the site of propagation due to the concept that this might produce a more effective propulsive action. In addition, colonic motor activity is now being defined as exhibiting *regional linkage* if sequential propagating sequences start at different sites but are in the same direction with overlapping side hole activity. It is believed that the amount of colonic activity that is regionally linked is directly related to the

efficacy of motor function and that increasing the percentage of linked propagating sequences should improve colonic performance. Following intervention with electrical therapy there was no increase in colonic regional linkage with an actual decrease seen with regards to retrograde activity (61% ± 10% vs. 33% ± 23% (mean ± SD)). There was however an increase in the proportion of regionally linked activity that in turn formed colonic complexes (a sequence of 3 or more regionally linked PS) following IFT. This was so for both antegrade and retrograde activity. This suggests that to a certain extent the increase in colonic propagating sequences is represented by disorganised activity; however, some subjects that did not exhibit any ability to form colonic complexes prior to intervention but did do so following therapy with electrical stimulation. It may be that more time is required for the colon to organise the increased activity which would correlate with the fact that some subjects seemed to experience a lag time between receiving IFT and experiencing clinical improvement.

None of the subjects reported any problems either during the insertion of the recording catheter or over the subsequent 24-hour recording period. The study confirms that following careful explanation and adequate preparation, recording catheters can be inserted straightforwardly and repositioned via an existing appendicostomy without the need for sedation or analgesia [76].

With regards to the bowel diary data, there was no significant change in frequency of defecation, soiling or abdominal pain after treatment with IFT. These results are similar to those found in chapter 6. Since patients are managed with

appendicostomies they have relatively few episodes of stooling and soiling and so data analysis is subsequently difficult. The subjects also reported relatively few episodes of abdominal pain pre-treatment.

All aspects of the current study were significantly hampered by the number of participants. With data only available for 5 subjects, it is hard to make meaningful statistical comparisons. With such small numbers, even the addition of an additional subject can lead to very different conclusions - had the full set of data been available for the 6th subject, then the same results (including the small increase in antegrade activity) may not have been evident.

In conclusion, this study shows that following treatment with transcutaneous interferential electrical therapy, subjects with STC have an increase in the total number of propagating sequences as measured by 24-hour continuous manometry, however, it is only a small increase and only with regards to antegrade propagating sequences. There is no change with regards to the site of origin, distance travelled or average amplitude for both antegrade and retrograde activity. There does, however, seem to be an increase in the amount of high amplitude propagating sequences in response to eating and waking. There was no effect on frequency of defecation, soiling or abdominal pain. The current study represents novel data that has not been previously reported in any study. Although findings are minimal, further investigation and participant recruitment is warranted in order to ascertain whether or not there is a potential clinical application for IFT in the management of children with slow transit constipation.

9. Discussion

9. Discussion

Chronic childhood constipation is a common and debilitating condition. Although the majority of children with constipation respond to simple measures, some unfortunately fail to gain any benefit from laxatives, behavioural therapy or intensive toileting programs. These children are faced with a life of infrequent defecation, intractable soiling and abdominal pain [19 20 279 299].

This thesis aimed to ascertain the affect on quality of life of longstanding chronic slow transit constipation and found that children described a significant impairment in their physical and psychosocial functioning when compared to age matched controls. It then sought to determine whether or not nuclear scintigraphy can be regarded as a reliable means of assessing colonic transit in children with STC and concluded that appropriate test-re-test reliability does appear to exist. The thesis then proposed to evaluate the potential application of transcutaneous electrical stimulation in the form of interferential therapy in the management of children with STC by means of a prospective, single blind, randomised controlled trial. It found that there was no effect on stool frequency or soiling but there was a small improvement in abdominal pain. Although there did not appear to be any improvement in QoL when comparing the two treatment arms, when looking solely at the group that received real therapy, there was significant improvement in both their physical and psychosocial QoL. When looking at colonic transit before and after intervention, there was a small, but consistent, decrease in colonic transit time after treatment with real IFT. Finally, the thesis considered the potential effect of IFT upon colonic activity as measured by colonic manometric catheters sited in an antegrade manner

through appendicostomies in children with pre-existing appendix stomas. This study showed that there was an increase in antegrade manometric activity, but no effect on all other recording parameters.

It is not only the child who is affected but also their parents and siblings as often the whole family schedule has to be based around ease of access to toilets and changing facilities. Any excursion, or overnight stay, that is out of the ordinary has to be carefully planned in advance in order to avoid potentially embarrassing situations. With this in mind it is perhaps unsurprising that in the study reported in chapter five, children with STC describe a significant deficit in their quality of life with both their physical and emotional functioning clearly affected [278]. What is also maybe unexpected, is that the level of quality of life that children with slow transit constipation and their parents depict is similar to that reported by children, and parents of children, with malignancy [222]. This highlights that although it is often perceived as a relatively benign condition, constipation is in fact extremely deleterious to both physical and mental health [260]. In association with the recognition of the importance of QoL evaluation in clinical research, there have been other recent studies that have sought to evaluate the effect of QoL in children with chronic constipation and soiling. A study by Grootenhuis *et al.* similarly reported that children with a higher frequency of soiling episodes described poorer emotional and social functioning [272]. Two recent reviews of the impact of constipation in children and adults (that both included the study reported in this thesis) concluded the impact of constipation on QoL is significant and comparable with other common chronic conditions, both gastrointestinal and non-gastrointestinal [331] [332]. They also

highlighted the fact that most existing QoL tools are not able to accurately assess the impact of constipation and soiling on QoL in children and that few studies have looked at the effect of treatment in the paediatric population. Further research in this area is evidently required and justified based on evidence to date.

There are currently a number of criteria that are utilised to diagnose subjects with slow transit constipation; clinical symptoms of constipation need to be associated with specific radiographic, and in some instances manometric, findings. It is important to be able to reliably diagnose and identify those who experience constipation secondary to slow colonic transit as it becoming more evident that they, unlike others, will not respond to conventional management. Children with chronic, treatment-resistant constipation therefore require to be separated into those with delayed global colonic transit and those with anorectal holdup. Colonic transit time has traditionally been assessed by radio-opaque marker studies, however their consistency in subjects with colonic inertia has been questioned [57 61]. In addition, there needs to be a dependable, objective, means of assessing response to treatment.

More recently, gastrointestinal transit time has been evaluated using nuclear scintigraphy [62-70]. This method has both been validated [138] and found to have satisfactory inter-observer reliability [298]. Nuclear transit studies (NTS) allow accurate assessment of regional colonic transit with multiple images of the colon being easily obtained with a relatively low radiation dose [147]. In addition, in contrast to marker studies, overlapping regions of the gastrointestinal tract do not pose a problem when viewing sequential radio-isotope images. Some studies have

suggested that there may be a difference between the passage of radioisotope and radio-opaque markers with the former possessing the ability to more accurately reflect the passage of physiological chyme [304]. It has also been proposed that indigestible solid particles do not move with a meal, and may not be handled by the colon in the same manner as stool [61].

There are, however, no studies that have evaluated the test-re-test reliability of nuclear scintigraphy over time. If indeed GITT is to be used as a consistent means of objective assessment following changes in therapy, then it important that any changes can reliably be attributed to the treatment and not to chance. The study described in chapter six, the first of its kind, demonstrates that in a state of colonic inertia, NTS are indeed reproducible and can therefore perhaps be relied upon as both a diagnostic tool and a means of assessing response to treatment. It must however be remembered that, despite their potential shortfalls in subjects with colonic inertia, the gold standard for assessing colonic transit time still remains radio-opaque marker studies and presently there are few centres that either have the ability, or choose, to use nuclear scintigraphy to evaluate colonic transit.

Currently, the treatment options for children with chronic constipation in whom conventional measures have failed are limited. In some the only remaining choice is surgical intervention in the form of either colonic resection of redundant, or dilated, bowel [121 333] or appendicostomy formation with subsequent instigation of antegrade colonic enemas in an attempt to achieve continence [126 128]. Both of these procedures are invasive and unfortunately, resultant clinical responses are variable. A recent

review of surgical options for treatment of constipation in children and adults highlighted the importance of patient selection and that surgery should be thought of as a last resort following exhaustion of all dietary, pharmacological and behavioural options [334].

Electrical therapy is a longstanding treatment modality that has been utilised, with varying success, for a multitude of complaints and ailments [165-167]. Transcutaneous electrical therapy is a well recognised treatment modality in children as it is painless, well-tolerated and can be administered in an out-patient, or even home, setting [199 335-337].

IFT is a form of electrical stimulation that involves the transcutaneous application, via electrodes, of two crossed, slightly out of phase, medium-frequency currents which produces an amplitude-modulated current effect within the tissues. The frequency, amplitude and pulse width of the output waveforms can all be regulated. Conventionally, currents within the range of 3,900 to 4,100Hz are used, as lower frequency currents can result in uncomfortable polarisation effects in the superficial tissues. Typically a quadripolar model is adopted where four electrodes are placed over the target area in such a distribution that their current paths cross directly over the relevant organ(s). IFT has been utilised, with significant success, in the management of both adults and children with detrusor instability [328]. As yet, its mechanism of action remains unknown however it is thought to act via means of neuromodulation.

Chapter 7 reports a randomised controlled trial assessing the potential use of IFT in the treatment of children with STC. The study found that subjects who received real IFT experienced no alteration in either the frequency of their stooling or soiling when compared to subjects who received placebo stimulation. Linear analysis however, showed a small decrease in soiling in those subjects who were randomised to receive real intervention. Both intergroup and linear analysis suggested a small improvement in abdominal pain in subjects in the real treatment arm.

Given that there appeared to be no effect on the frequency of either spontaneous stooling or timed 'sit' stooling, it might be fair to assume that IFT has no prospective role in the treatment of children with STC. Alternatively, in this highly selected group of subjects for whom treatment options, apart from surgical intervention, are becoming limited, if there is any potential benefit from a non-invasive therapy than full evaluation should be performed. The current study had small numbers and many of the outcome measures were difficult to objectively assess. Children with STC, unlike the majority of children with chronic constipation, do not always display infrequent defecation. Instead, they often have frequent passage of pasty, poor quality stools. In an individual subject, a decrease in stool frequency, perhaps associated with an improvement in stool consistency, may represent a better clinical outcome than an increase in stooling.

Since electrical therapy is a recognised treatment modality for pain, and has indeed be utilised with reported success in subjects with functional abdominal pain [199], it is unclear whether or not this outcome was due to an improvement in the underlying

gastrointestinal pathology or simply due to electrically induced neuromodulation of painful stimuli.

Children who received real IFT reported an improvement in their quality of life when paired analysis before and after treatment was performed in each treatment arm. This was reflected by an increase in both self-perceived physical and psychosocial scores. Several studies have now highlighted the deleterious effect of abdominal pain and soiling associated with constipation in children [242 272 277 278]. The change in QoL seen in the real intervention group could potentially be linked to the small improvement in these subjects in association with these symptoms. It must again be remembered, however, that the study contained small numbers of participants in each treatment arm. If, however, the post-intervention data are compared to the control values obtained in chapter 5, the real treatment group no longer display significantly poorer QoL than the control subjects (mean 86.0 vs. 81.1; $p = 0.09$) whereas the placebo group still do (mean 86.0 vs. 78.1; $p = 0.003$).

Although it is essential for any successful therapy to produce an improvement in clinical symptoms, it is also important that it evokes some kind of objective, quantifiable response. Children with STC have characteristic, reproducible patterns in their colonic motility with regards to nuclear transit studies (NTS). Those subjects in the real treatment arm of the study had a small significant decrease in their colonic transit time, as measured by nuclear scintigraphy suggesting that IFT might have some effect upon colonic motility. Unfortunately, the numbers of studies available for analysis are small and so the significance of the findings should be interpreted

with caution. The clinical significance of the small increase in colonic transit is also questionable, however, the studies were performed after only 12 treatment sessions with IFT. It remains unknown as to whether or not a prolonged course of treatment might further decrease colonic transit time or the inclusion or more data might negate any positive findings. As with the other studies described, there is the need for further investigation to be executed.

The final study investigated the effects of IFT on colonic activity as measured by colonic manometry. This, again, is an objective means of assessing any effect of IFT upon colonic function. However unfortunately, the number of subjects available for recruitment was even smaller than those in the previous studies. The only consistent effect of IFT appeared to be an increase in antegrade colonic activity. However, some subjects post intervention also appeared to have developed 'normal' physiological responses to waking and/or eating along with an overall increase in their high amplitude activity. As with the previous studies, although the results are, at best, inconclusive any positive findings warrant the instigation of additional investigation of IFT as an adjunctive treatment modality.

The mechanisms by which IFT may have any potential effect remain unclear. Possible means of action include alteration of activity of the colonic pacemaker interstitial cells of Cajal (ICC) or changes in the balance of excitatory and inhibitory neuronal transmission, either due to alterations in neurotransmitter release or due to augmented nerve fibre activity. A recent review by Ward of transcutaneous electrical stimulation using alternating current sought to offer some insight into its

mechanism of action [338]. He suggests that claims that cross-modulated current delivered via quadripolar stimulation (rather than bipolar stimulation) produces stimulation at greater depth are unsubstantiated and that 'current spreading' means that there will not be a region at the centre of intersection of the currents where maximum stimulation occurs. This is due to current flow between adjacent electrodes occurring because of shorter-distance, lower-resistance pathways. The author also highlights that with alternating current, the biphasic waveform can be sinusoidal or rectangular and the current can be delivered continuously, in bursts or in sinusoidally modulated bursts; in total there are 5 different parameters that need to be specified in order to describe an IFT waveform. As a consequence, the greater number of current parameters that exist, the greater the number of possible treatment permutations and combinations that exist. In addition, it remains unknown what the optimum treatment regimen entails with regards to treatment frequency, duration of treatment and electrode placement.

In the current study, electrodes were placed paraspinally at the level of T9-L2 and on the abdominal wall at the level of the umbilicus. In this position, current could potentially be exerting influence upon local sensory and motor nerves in the skin, spinal nerves, sympathetic and parasympathetic nerves, enteric nerves or cells (ICC or smooth muscles) within the bowel wall. The lack of immediate response (i.e. defecation) during stimulation suggests that any effect is not via direct stimulation of intestinal smooth muscle.

9.1 Future aims

Interferential therapy represents a painless, well-tolerated, non-invasive and relatively inexpensive form of therapy that may have a potential clinical application in this sub-group of children with chronic constipation. Further studies are required to attempt to quantify its mode of action and to delineate optimum treatment parameters. If these can be more accurately determined then electrical therapy may once again become a widely accepted and applied therapeutic modality.

9.1.1 Animal studies

IFT utilises the transcutaneous application of current and as yet the degree of tissue penetration is unknown; this knowledge could provide a vital key as to its means of action. Animal studies involving the use of implantable electrodes have been suggested in order to attempt to ascertain both the depth of attainable dissemination of current and also any changes in actual electrical conduction within tissues. If, in the context of transcutaneously applied current, implanted electrodes were able to demonstrate a direct change in colonic electrical activity then neuromodulation would seem a less likely mechanism of action. Animal studies are not without their own problems with one obvious discrepancy being that they currently involve disease free models. In addition, in order to implant electrodes in the bowel wall, not only is general anaesthesia required but the bowel has to be both exposed and handled; factors that have a well-documented association with intestinal stasis. Therefore, in order to adequately determine whether or not colonic electrical activity is affected, studies need to be designed to ensure that animals are appropriately

recovered following electrode placement, before transcutaneous stimulation and subsequent recording is commenced.

9.1.2 Different modes of current delivery

Although IFT is relatively inexpensive, it is not available in all centres and usually requires to be administered by a qualified practitioner - most often a physiotherapist. There exists a much more widely available, cheaper and 'home friendly' form of electrical therapy, namely TENS. In addition to determining the optimum treatment parameters of IFT, it is important to determine whether or not similar results can be achieved following the administration of TENS.

In addition, since the completion of this thesis, there has become available a portable, battery-operated, home treatment amenable form of IFT. A pilot study assessing 11 children having daily stimulation delivered at home via a portable IFT unit found that defecation increased in 9 of the 11 subjects [339].

9.1.3 Other clinical applications

This study concentrated only on children with intestinal dysmotility secondary to slow transit constipation. There are many other conditions resulting in delayed passage of intestinal contents that may also benefit from electrical therapy. In particular, although for some children with Hirschsprung's disease surgical resection of the aganglionic bowel is curative, there are many in whom refractory constipation is an ongoing challenge. These children would make excellent subjects for ongoing research since treatment options are limited and often ineffectual.

If a clear benefit can be demonstrated by the clinical application of electrical therapy then not only could it be applied in cases of chronic intestinal dysmotility, but perhaps also in the acute setting where a prolonged ileus is the result of either an underlying condition (i.e. sepsis, burns, drugs) or a post-operative complication. Improvement in intestinal function in many of these patients could result in an increase in their nutritional state and immune function along with decreasing their time to recovery and subsequent discharge from hospital.

In conclusion, this study describes a novel approach to the evaluation and subsequent treatment strategies for children with slow transit constipation. It presents evidence that routine assessment of children with constipation should involve appraisal of QoL and that nuclear scintigraphy is an alternative, reliable means of assessing colonic transit. It also provides data that support the further assessment of an entirely novel treatment mode - transcutaneous electrical stimulation with interferential therapy.

References

1. Candelli M, Nista EC, Zocco MA, Gasbarrini A. Idiopathic chronic constipation: pathophysiology, diagnosis and treatment. *Hepatogastroenterology* 2001;48(40):1050-7.
2. Milla P, Cucchiara S, DiLorenzo C, Rivera NM, Rudolph C, Tomomasa T. Motility disorders in childhood: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35 Suppl 2:S187-95.
3. Sondheimer J. Constipation: is there a new approach? *J Pediatr Gastroenterol Nutr* 2002;34(4):357-8.
4. Youssef NN, Di Lorenzo C. Childhood constipation: evaluation and treatment. *J Clin Gastroenterol* 2001;33(3):199-205.
5. Villarreal J, Sood M, Zangen T, Flores A, Michel R, Reddy N, et al. Colonic diversion for intractable constipation in children: colonic manometry helps guide clinical decisions. *J Pediatr Gastroenterol Nutr* 2001;33(5):588-91.
6. Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2006;43(3):e1-13.
7. Benninga M, Candy DC, Catto-Smith AG, Clayden G, Loening-Baucke V, Di Lorenzo C, et al. The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. *J Pediatr Gastroenterol Nutr* 2005;40(3):273-5.
8. Fontana M, Bianchi C, Cataldo F, Conti Nibali S, Cucchiara S, Gobio Casali L, et al. Bowel frequency in healthy children. *Acta Paediatr Scand* 1989;78(5):682-4.
9. Tagart RE. The anal canal and rectum: their varying relationship and its effect on anal continence. *Dis Colon Rectum* 1966;9(6):449-52.
10. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;130(5):1377-90.
11. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006;130(5):1527-37.
12. Partin JC, Hamill SK, Fischel JE, Partin JS. Painful defecation and fecal soiling in children. *Pediatrics* 1992;89(6 Pt 1):1007-9.
13. Youssef NN, Di Lorenzo C. Treatment Options for Refractory Childhood Constipation. *Curr Treat Options Gastroenterol* 2002;5(5):377-387.
14. Staiano A, Andreotti MR, Greco L, Basile P, Auricchio S. Long-term follow-up of children with chronic idiopathic constipation. *Dig Dis Sci* 1994;39(3):561-4.
15. Robinson M, Roberton D. *Practical Paediatrics* 2003;5th edn. Churchill Livingston, Melbourne.
16. El-Salhy M. Chronic idiopathic slow transit constipation: pathophysiology and management. *Colorectal Dis* 2003;5(4):288-96.
17. Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. *Gut* 1986;27(1):41-8.

18. Watier A, Devroede G, Duranceau A, Abdel-Rahman M, Duguay C, Forand MD, et al. Constipation with colonic inertia. A manifestation of systemic disease? *Dig Dis Sci* 1983;28(11):1025-33.
19. Benninga MA, Buller HA, Tytgat GN, Akkermans LM, Bossuyt PM, Taminiau JA. Colonic transit time in constipated children: does pediatric slow-transit constipation exist? *J Pediatr Gastroenterol Nutr* 1996;23(3):241-51.
20. Southwell BR, King SK, Hutson JM. Chronic constipation in children: organic disorders are a major cause. *J Paediatr Child Health* 2005;41(1-2):1-15.
21. Reynolds JC, Ouyang A, Lee CA, Baker L, Sunshine AG, Cohen S. Chronic severe constipation. Prospective motility studies in 25 consecutive patients. *Gastroenterology* 1987;92(2):414-20.
22. van der Sijp JR, Kamm MA, Nightingale JM, Britton KE, Granowska M, Mather SJ, et al. Disturbed gastric and small bowel transit in severe idiopathic constipation. *Dig Dis Sci* 1993;38(5):837-44.
23. Bassotti G, Stanghellini V, Chiarioni G, Germani U, De Giorgio R, Vantini I, et al. Upper gastrointestinal motor activity in patients with slow-transit constipation. Further evidence for an enteric neuropathy. *Dig Dis Sci* 1996;41(10):1999-2005.
24. Panagamuwa B, Kumar D, Ortiz J, Keighley MR. Motor abnormalities in the terminal ileum of patients with chronic idiopathic constipation. *Br J Surg* 1994;81(11):1685-8.
25. Penning C, Gielkens HA, Hemelaar M, Delemarre JB, Bemelman WA, Lamers CB, et al. Prolonged ambulatory recording of antroduodenal motility in slow-transit constipation. *Br J Surg* 2000;87(2):211-7.
26. Bassotti G, Villanacci V. Slow transit constipation: a functional disorder becomes an enteric neuropathy. *World J Gastroenterol* 2006;12(29):4609-13.
27. Altomare D, Pilot MA, Scott M, Williams N, Rubino M, Ilincic L, et al. Detection of subclinical autonomic neuropathy in constipated patients using a sweat test. *Gut* 1992;33(11):1539-43.
28. Raethjen J, Pilot MA, Knowles C, Warner G, Anand P, Williams N. Selective autonomic and sensory deficits in slow transit constipation. *J Auton Nerv Syst* 1997;66(1-2):46-52.
29. Knowles CH, Scott SM, Lunniss PJ. Slow transit constipation: a disorder of pelvic autonomic nerves? *Dig Dis Sci* 2001;46(2):389-401.
30. Knowles CH, Scott SM, Wellmer A, Misra VP, Pilot MA, Williams NS, et al. Sensory and autonomic neuropathy in patients with idiopathic slow-transit constipation. *Br J Surg* 1999;86(1):54-60.
31. Preston DM, Hawley PR, Lennard-Jones JE, Todd IP. Results of colectomy for severe idiopathic constipation in women (Arbuthnot Lane's disease). *Br J Surg* 1984;71(7):547-52.
32. Kamm MA, Hawley PR, Lennard-Jones JE. Outcome of colectomy for severe idiopathic constipation. *Gut* 1988;29(7):969-73.
33. Walsh PV, Peebles-Brown DA, Watkinson G. Colectomy for slow transit constipation. *Ann R Coll Surg Engl* 1987;69(2):71-5.
34. Krishnamurthy S, Schuffler MD, Rohrmann CA, Pope CE, 2nd. Severe idiopathic constipation is associated with a distinctive abnormality of the colonic myenteric plexus. *Gastroenterology* 1985;88(1 Pt 1):26-34.

35. Koch TR, Carney JA, Go L, Go VL. Idiopathic chronic constipation is associated with decreased colonic vasoactive intestinal peptide. *Gastroenterology* 1988;94(2):300-10.
36. Dolk A, Broden G, Holmstrom B, Johansson C, Schultzberg M. Slow transit chronic constipation (Arbuthnot Lane's disease). An immunohistochemical study of neuropeptide-containing nerves in resected specimens from the large bowel. *Int J Colorectal Dis* 1990;5(4):181-7.
37. Lincoln J, Crowe R, Kamm MA, Burnstock G, Lennard-Jones JE. Serotonin and 5-hydroxyindoleacetic acid are increased in the sigmoid colon in severe idiopathic constipation. *Gastroenterology* 1990;98(5 Pt 1):1219-25.
38. Tzavella K, Riepl RL, Klauser AG, Voderholzer WA, Schindlbeck NE, Muller-Lissner SA. Decreased substance P levels in rectal biopsies from patients with slow transit constipation. *Eur J Gastroenterol Hepatol* 1996;8(12):1207-11.
39. Sjolund K, Fasth S, Ekman R, Hulten L, Jiborn H, Nordgren S, et al. Neuropeptides in idiopathic chronic constipation (slow transit constipation). *Neurogastroenterol Motil* 1997;9(3):143-50.
40. Tomita R, Fujisaki S, Ikeda T, Fukuzawa M. Role of nitric oxide in the colon of patients with slow-transit constipation. *Dis Colon Rectum* 2002;45(5):593-600.
41. Cajal SR. Sur les ganglions et plexus nerveux de l'intestin. *C R Soc Biol* 1893:217-23.
42. Tong WD, Liu BH, Zhang LY, Zhang SB. [Study on distribution of interstitial cells of Cajal in the sigmoid colon of patients with slow transit constipation]. *Zhonghua Wai Ke Za Zhi* 2004;42(14):853-6.
43. Hagger R, Gharaie S, Finlayson C, Kumar D. Distribution of the interstitial cells of Cajal in the human anorectum. *J Auton Nerv Syst* 1998;73(2-3):75-9.
44. Rumessen JJ, Thuneberg L. Pacemaker cells in the gastrointestinal tract: interstitial cells of Cajal. *Scand J Gastroenterol Suppl* 1996;216:82-94.
45. Thuneberg L. Interstitial cells of Cajal: intestinal pacemaker cells? *Adv Anat Embryol Cell Biol* 1982;71:1-130.
46. Hasler WL. Is constipation caused by a loss of colonic interstitial cells of Cajal? *Gastroenterology* 2003;125(1):264-5; discussion 265-6.
47. Battaglia E, Bassotti G, Bellone G, Dughera L, Serra AM, Chiusa L, et al. Loss of interstitial cells of Cajal network in severe idiopathic gastroparesis. *World J Gastroenterol* 2006;12(38):6172-7.
48. He CL, Burgart L, Wang L, Pemberton J, Young-Fadok T, Szurszewski J, et al. Decreased interstitial cell of cajal volume in patients with slow-transit constipation. *Gastroenterology* 2000;118(1):14-21.
49. Jain D, Moussa K, Tandon M, Culpepper-Morgan J, Proctor DD. Role of interstitial cells of Cajal in motility disorders of the bowel. *Am J Gastroenterol* 2003;98(3):618-24.
50. Kenny SE, Connell MG, Rintala RJ, Vaillant C, Edgar DH, Lloyd DA. Abnormal colonic interstitial cells of Cajal in children with anorectal malformations. *J Pediatr Surg* 1998;33(1):130-2.
51. Lyford GL, He CL, Soffer E, Hull TL, Strong SA, Senagore AJ, et al. Pan-colonic decrease in interstitial cells of Cajal in patients with slow transit constipation. *Gut* 2002;51(4):496-501.

52. Rolle U, Piotrowska AP, Nemeth L, Puri P. Altered distribution of interstitial cells of Cajal in Hirschsprung disease. *Arch Pathol Lab Med* 2002;126(8):928-33.
53. Sabri M, Barksdale E, Di Lorenzo C. Constipation and lack of colonic interstitial cells of Cajal. *Dig Dis Sci* 2003;48(5):849-53.
54. Shafik A, Shafik AA, El-Sibai O, Shafik IA. Interstitial cells of cajal in patients with constipation due to total colonic inertia. *J Invest Surg* 2006;19(3):147-53.
55. Catto-Smith AG. 5. Constipation and toileting issues in children. *Med J Aust* 2005;182(5):242-6.
56. Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. *Gastroenterology* 1987;92(1):40-7.
57. Bouchoucha M, Devroede G, Arhan P, Strom B, Weber J, Cugnenc PH, et al. What is the meaning of colorectal transit time measurement? *Dis Colon Rectum* 1992;35(8):773-82.
58. Arhan P, Devroede G, Jehannin B, Lanza M, Faverdin C, Dornic C, et al. Segmental colonic transit time. *Dis Colon Rectum* 1981;24(8):625-9.
59. Papadopoulou A, Clayden GS, Booth IW. The clinical value of solid marker transit studies in childhood constipation and soiling. *Eur J Pediatr* 1994;153(8):560-4.
60. Wagener S, Shankar KR, Turnock RR, Lamont GL, Baillie CT. Colonic transit time--what is normal? *J Pediatr Surg* 2004;39(2):166-9; discussion 166-9.
61. Nam YS, Pikarsky AJ, Wexner SD, Singh JJ, Weiss EG, Nogueras JJ, et al. Reproducibility of colonic transit study in patients with chronic constipation. *Dis Colon Rectum* 2001;44(1):86-92.
62. Maurer AH, Parkman HP. Update on gastrointestinal scintigraphy. *Semin Nucl Med* 2006;36(2):110-8.
63. Rao S, Lele V. Scintigraphy of the small intestine: a simplified standard for study of transit with reference to normal values. *Eur J Nucl Med Mol Imaging* 2002;29(7):971; author reply 971-2.
64. Bonapace ES, Maurer AH, Davidoff S, Krevsky B, Fisher RS, Parkman HP. Whole gut transit scintigraphy in the clinical evaluation of patients with upper and lower gastrointestinal symptoms. *Am J Gastroenterol* 2000;95(10):2838-47.
65. Eising EG, von der Ohe MR. Differentiation of prolonged colonic transit using scintigraphy with indium-111-labeled polystyrene pellets. *J Nucl Med* 1998;39(6):1062-6.
66. McLean RG, King DW, Talley NA, Tait AD, Freiman J. The utilization of colon transit scintigraphy in the diagnostic algorithm for patients with chronic constipation. *Dig Dis Sci* 1999;44(1):41-7.
67. McLean R, Smart R, Barbagallo S, King D, Stein P, Talley N. Colon transit scintigraphy using oral indium-111-labeled DTPA. Can scan pattern predict final diagnosis? *Dig Dis Sci* 1995;40(12):2660-8.
68. Maurer AH, Krevsky B. Whole-gut transit scintigraphy in the evaluation of small-bowel and colon transit disorders. *Semin Nucl Med* 1995;25(4):326-38.

69. Cook BJ, Lim E, Cook D, Hughes J, Chow CW, Stanton MP, et al. Radionuclear transit to assess sites of delay in large bowel transit in children with chronic idiopathic constipation. *J Pediatr Surg* 2005;40(3):478-83.
70. Zuccarello B, Romeo C, Scalfari G, Impellizzeri P, Montalto AS, D'Oppido D, et al. Scintigraphic evaluation of colonic motility in patients with anorectal malformations and constipation. *J Pediatr Surg* 2006;41(2):310-3.
71. Neville HL, Cox CS. Hirschsprung Disease. *www.emedicine.com* 2006.
72. Whitehouse FR, Kernohan JW. The myenteric plexus in congenital megacolon. *Arch Int Med* 1948;82:75.
73. Stanton MP, Hengel PT, Southwell BR, Chow CW, Keck J, Hutson JM, et al. Cholinergic transmission to colonic circular muscle of children with slow-transit constipation is unimpaired, but transmission via NK2 receptors is lacking. *Neurogastroenterol Motil* 2003;15(6):669-78.
74. Hutson JM, Chow CW, Borg J. Intractable constipation with a decrease in substance P-immunoreactive fibres: is it a variant of intestinal neuronal dysplasia? *J Pediatr Surg* 1996;31(4):580-3.
75. Hutson JM, Chow CW, Hurley MR, Uemura S, Wheatley JM, Catto-Smith AG. Deficiency of substance P-immunoreactive nerve fibres in children with intractable constipation: a form of intestinal neuronal dysplasia. *J Paediatr Child Health* 1997;33(3):187-9.
76. Stanton MP, Hutson JM, Simpson D, Oliver MR, Southwell BR, Dinning P, et al. Colonic manometry via appendicostomy shows reduced frequency, amplitude, and length of propagating sequences in children with slow-transit constipation. *J Pediatr Surg* 2005;40(7):1138-45.
77. Di Lorenzo C, Flores AF, Reddy SN, Hyman PE. Use of colonic manometry to differentiate causes of intractable constipation in children. *J Pediatr* 1992;120(5):690-5.
78. Godbole K. Many faces of Hirschsprung's disease. *Indian Pediatr* 2004;41(11):1115-23.
79. Okamoto EU. Embryogenesis of intramural ganglia of the gut and its relation to Hirschsprung's disease. *J Pediatr Surg* 1967;2:437-443.
80. Lyford G, Foxx-Orenstein A. Chronic Intestinal Pseudoobstruction. *Curr Treat Options Gastroenterol* 2004;7(4):317-325.
81. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo C. Long-term outcome of congenital intestinal pseudoobstruction. *Dig Dis Sci* 2002;47(10):2298-305.
82. Meier-Ruge W. [Casuistic of colon disorder with symptoms of Hirschsprung's disease (author's transl)]. *Verhandlungen der Deutschen Gesellschaft fur Pathologie* 1971;55:506-10.
83. Fadda B, Maier WA, Meier-Ruge W, Scharli A, Daum R. [Neuronal intestinal dysplasia. Critical 10-years' analysis of clinical and biopsy diagnosis]. *Z Kinderchir* 1983;38(5):305-11.
84. Galvez Y, Skaba R, Vajtrova R, Frantlova A, Herget J. Evidence of secondary neuronal intestinal dysplasia in a rat model of chronic intestinal obstruction. *J Invest Surg* 2004;17(1):31-9.
85. Martucciello G, Torre M, Pini Prato A, Lerone M, Campus R, Leggio S, et al. Associated anomalies in intestinal neuronal dysplasia. *J Pediatr Surg* 2002;37(2):219-23.

86. Scharli AF, Meier-Ruge W. Localized and disseminated forms of neuronal intestinal dysplasia mimicking Hirschsprung's disease. *J Pediatr Surg* 1981;16(2):164-70.
87. Lake BD. Intestinal neuronal dysplasia. Why does it only occur in parts of Europe? *Virchows Arch* 1995;426(6):537-9.
88. Lumb PD, Moore L. Back to the drawing board. Intestinal neuronal dysplasia type B: not a histological entity yet. *Virchows Arch* 1998;432(2):99-102.
89. Lumb PD, Moore L. Are giant ganglia a reliable marker of intestinal neuronal dysplasia type B (IND B)? *Virchows Arch* 1998;432(2):103-6.
90. Berry CL. Intestinal neuronal dysplasia: does it exist or has it been invented? *Virchows Arch A Pathol Anat Histopathol* 1993;422(3):183-4.
91. Koletzko S, Jesch I, Faus-Kebler T, Briner J, Meier-Ruge W, Muntefering H, et al. Rectal biopsy for diagnosis of intestinal neuronal dysplasia in children: a prospective multicentre study on interobserver variation and clinical outcome. *Gut* 1999;44:853-861.
92. Shirasawa S, Yunker AM, Roth KA, Brown GA, Horning S, Korsmeyer SJ. Enx (Hox11L1)-deficient mice develop myenteric neuronal hyperplasia and megacolon. *Nat Med* 1997;3(6):646-50.
93. Tiffin ME, Chandler LR, Faber HK. Localized abscence of the ganglion cells of myenteric plexus in congenital megacolon. *AM J Dis Child* 1940;59:1071-82.
94. Martucciello G, Pini Prato A, Puri P, Holschneider AM, Meier-Ruge W, Jasonni V, et al. Controversies concerning diagnostic guidelines for anomalies of the enteric nervous system: a report from the fourth International Symposium on Hirschsprung's disease and related neurocristopathies. *J Pediatr Surg* 2005;40(10):1527-31.
95. Taguchi T, Masumoto K, Ieiri S, Nakatsuji T, Akiyoshi J. New classification of hypoganglionosis: congenital and acquired hypoganglionosis. *J Pediatr Surg* 2006;41(12):2046-51.
96. Marlett JA, McBurney MI, Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2002;102(7):993-1000.
97. Loening-Baucke V, Miele E, Staiano A. Fiber (glucomannan) is beneficial in the treatment of childhood constipation. *Pediatrics* 2004;113(3 Pt 1):e259-64.
98. Burkitt DP, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. *Lancet* 1972;2(7792):1408-12.
99. Voderholzer WA, Schatke W, Muhldorfer BE, Klauser AG, Birkner B, Muller-Lissner SA. Clinical response to dietary fiber treatment of chronic constipation. *Am J Gastroenterol* 1997;92(1):95-8.
100. Badiali D, Corazziari E, Habib FI, Tomei E, Bausano G, Magrini P, et al. Effect of wheat bran in treatment of chronic nonorganic constipation. A double-blind controlled trial. *Dig Dis Sci* 1995;40(2):349-56.
101. Chung BD, Parekh U, Sellin JH. Effect of increased fluid intake on stool output in normal healthy volunteers. *J Clin Gastroenterol* 1999;28(1):29-32.
102. Young RJ, Beerman LE, Vanderhoof JA. Increasing oral fluids in chronic constipation in children. *Gastroenterol Nurs* 1998;21(4):156-61.

103. Barr RG, Levine MD, Wilkinson RH, Mulvihill D. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. *Clin Pediatr (Phila)* 1979;18(11):674, 676, 677-9, passim.
104. Wald A. Constipation. *Med Clin North Am* 2000;84(5):1231-46, ix.
105. Candy DC, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. *Arch Dis Child* 2009;94(2):156-160.
106. Nusko G, Schneider B, Ernst H, Wittekind C, Hahn EG. Melanosis coli--a harmless pigmentation or a precancerous condition? *Z. Gastroenterol* 1997;35(5):313-8.
107. Voderholzer WA, Morena MA, Schindlbeck NE. The influence of bisacodyl on human colon motility in vitro. *Gastroenterology* 2000;118(A838):21-4.
108. Suzuki M, Morita T, Iwamoto T. Diversity of Cl(-) channels. *Cell Mol Life Sci* 2006;63(1):12-24.
109. Lacy BE, Campbell Levy L. Lubiprostone: a chloride channel activator. *J Clin Gastroenterol* 2007;41(4):345-51.
110. Raqhunath N, Glassman MS, Halata MS, Berezin SH, Stewart JM, Medow MS. Anorectal motility abnormalities in children with encopresis and chronic constipation. *J Paediatr* 2011;158(2):293-6.
111. Benninga MA, Buller HA, Taminiau JA. Biofeedback training in chronic constipation. *Arch Dis Child* 1993;68(1):126-9.
112. Olness K, McParland FA, Piper J. Biofeedback: a new modality in the management of children with fecal soiling. *J Pediatr* 1980;96(3 Pt 1):505-9.
113. Weber J, Ducrotte P, Touchais JY, Roussignol C, Denis P. Biofeedback training for constipation in adults and children. *Dis Colon Rectum* 1987;30(11):844-6.
114. Wexner SD, Cheape JD, Jorge JM, Heymen S, Jagelman DG. Prospective assessment of biofeedback for the treatment of paradoxical puborectalis contraction. *Dis Colon Rectum* 1992;35(2):145-50.
115. Griffiths P, Dunn S, Evans A, Smith D, Bradnam M. Portable biofeedback apparatus for treatment of anal sphincter dystonia in childhood soiling and constipation. *J Med Eng Technol* 1999;23(3):96-101.
116. Nolan T, Catto-Smith T, Coffey C, Wells J. Randomised controlled trial of biofeedback training in persistent encopresis with anismus. *Arch Dis Child* 1998;79(2):131-5.
117. Loening-Baucke V. Biofeedback treatment for chronic constipation and encopresis in childhood: long-term outcome. *Pediatrics* 1995;96(1 Pt 1):105-10.
118. Loening-Baucke V. Biofeedback training in children with functional constipation. A critical review. *Dig Dis Sci* 1996;41(1):65-71.
119. Sunic-Omejc M, Mihanovic M, Bilic A, Jurcic D, Restek-Petrovic B, Maric N, et al. Efficiency of biofeedback therapy for chronic constipation in children. *Coll Antropol* 2002;26 Suppl:93-101.
120. Simpson BB, Ryan DP, Schnitzer JJ, Flores A, Doody DP. Surgical evaluation and management of refractory constipation in older children. *J Pediatr Surg* 1996;31(8):1040-2.
121. Ghosh S, Papachrysostomou M, Batool M, Eastwood MA. Long-term results of subtotal colectomy and evidence of noncolonic involvement in patients with

idiopathic slow-transit constipation. *Scand J Gastroenterol* 1996;31(11):1083-91.
122. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. *Ann Surg* 1999;230(5):627-38.
123. Lundin E, Karlbom U, Pahlman L, Graf W. Outcome of segmental colonic resection for slow-transit constipation. *Br J Surg* 2002;89(10):1270-4.
124. Wexner SD, Daniel N, Jagelman DG. Colectomy for constipation: physiologic investigation is the key to success. *Dis Colon Rectum* 1991;34(10):851-6.
125. Malone PS, Curry JI, Osborne A. The antegrade continence enema procedure why, when and how? *World J Urol* 1998;16(4):274-8.
126. King SK, Sutcliffe JR, Southwell BR, Chait PG, Hutson JM. The antegrade continence enema successfully treats idiopathic slow-transit constipation. *J Pediatr Surg* 2005;40(12):1935-40.
127. Marshall J, Hutson JM, Anticich N, Stanton MP. Antegrade continence enemas in the treatment of slow-transit constipation. *J Pediatr Surg* 2001;36(8):1227-30.
128. Stanton MP, Shin YM, Hutson JM. Laparoscopic placement of the Chait cecostomy device via appendicostomy. *J Pediatr Surg* 2002;37(12):1766-7.
129. Agnarsson U, Warde C, McCarthy G, Evans N. Perianal appearances associated with constipation. *Arch Dis Child* 1990;65(11):1231-4.
130. Benninga M, Voskuijl WP, Akkerhuis GW, Taminiau JA, Buller HA. Colonic transit times and behaviour profiles in children with defecation disorders. *Arch Dis Child* 2004;89(1):13-6.
131. Hinton JM, Lennard-Jones JE, Young AC. A new method for studying gut transit times using radioopaque markers. *Gut* 1969;10(10):842-7.
132. Gutierrez C, Marco A, Nogales A, Tebar R. Total and segmental colonic transit time and anorectal manometry in children with chronic idiopathic constipation. *J Pediatr Gastroenterol Nutr* 2002;35(1):31-8.
133. Lundin E, Karlbom U, Westlin JE, Kairemo K, Jung B, Husin S, et al. Scintigraphic assessment of slow transit constipation with special reference to right- or left-sided colonic delay. *Colorectal Dis* 2004;6(6):499-505.
134. Notghi A, Hutchinson R, Kumar D, Tulley N, Harding LK. Use of geometric center and parametric images in scintigraphic colonic transit studies. *Gastroenterology* 1994;107(5):1270-7.
135. Krevsky B, Malmud LS, D'Ercole F, Maurer AH, Fisher RS. Colonic transit scintigraphy. A physiologic approach to the quantitative measurement of colonic transit in humans. *Gastroenterology* 1986;91(5):1102-12.
136. Park MI, Ferber I, Camilleri M, Allenby K, Trillo R, Burton D, et al. Effect of atilmotin on gastrointestinal transit in healthy subjects: a randomized, placebo-controlled study. *Neurogastroenterol Motil* 2006;18(1):28-36.
137. Stubbs JB, Valenzuela GA, Stubbs CC, Croft BY, Teates CD, Plankey MW, et al. A noninvasive scintigraphic assessment of the colonic transit of nondigestible solids in man. *J Nucl Med* 1991;32(7):1375-81.
138. Cremonini F, Mullan BP, Camilleri M, Burton DD, Rank MR. Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. *Aliment Pharmacol Ther* 2002;16(10):1781-90.
139. Krevsky B, Maurer AH, Niewiarowski T, Cohen S. Effect of verapamil on human intestinal transit. *Dig Dis Sci* 1992;37(6):919-24.

140. Roberts JP, Newell MS, Deeks JJ, Waldron DW, Garvie NW, Williams NS. Oral [111In]DTPA scintigraphic assessment of colonic transit in constipated subjects. *Dig Dis Sci* 1993;38(6):1032-9.
141. Proano M, Camilleri M, Phillips SF, Brown ML, Thomforde GM. Transit of solids through the human colon: regional quantification in the unprepared bowel. *Am J Physiol* 1990;258(6 Pt 1):G856-62.
142. McLean RG, Smart RC, Lubowski DZ, King DW, Barbagallo S, Talley NA. Oral colon transit scintigraphy using indium-111 DTPA: variability in healthy subjects. *Int J Colorectal Dis* 1992;7(4):173-6.
143. Tota G, Messina M, Meucci D, Piro E, Di Maggio G, Garzi A, et al. [Use of radionuclides in the evaluation of intestinal transit time in children with idiopathic constipation]. *Pediatr Med Chir* 1998;20(1):63-6.
144. Graff J, Brinch K, Madsen JL. Gastrointestinal mean transit times in young and middle-aged healthy subjects. *Clin Physiol* 2001;21(2):253-9.
145. Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. *Scand J Gastroenterol* 2003;38(1):36-42.
146. Zaslavsky C, De Barros SG, Gruber AC, MacIel AC, Da Silveira TR. Chronic functional constipation in adolescents: clinical findings and motility studies. *J Adolesc Health* 2004;34(6):517-22.
147. van der Sijp JR, Kamm MA, Nightingale JM, Britton KE, Mather SJ, Morris GP, et al. Radioisotope determination of regional colonic transit in severe constipation: comparison with radio opaque markers. *Gut* 1993;34(3):402-8.
148. Southwell BR, Clarke MC, Sutcliffe JR, Hutson J. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. *Pediatr Surg Int* 2009;25(7):559-72.
149. Zaslavsky C, da Silveira TR, Maguilnik I. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. *J Pediatr Gastroenterol Nutr* 1998;27(2):138-42.
150. Corazziari E, Cucchiara S, Staiano A, Romaniello G, Tamburrini O, Torsoli A, et al. Gastrointestinal transit time, frequency of defecation, and anorectal manometry in healthy and constipated children. *J Pediatr* 1985;106(3):379-82.
151. Bautista Casasnovas A, Varela Cives R, Villanueva Jeremias A, Castro-Gago M, Cadranel S, Tojo Sierra R. Measurement of colonic transit time in children. *J Pediatr Gastroenterol Nutr* 1991;13(1):42-5.
152. Chaussade S, Roche H, Khyari A, Couturier D, Guerre J. [Measurement of colonic transit time: description and validation of a new method]. *Gastroenterol Clin Biol* 1986;10(5):385-9.
153. Cucchiara S, Coremans G, Staiano A, Corazziari E, Romaniello G, Di Lorenzo C, et al. Gastrointestinal transit time and anorectal manometry in children with fecal soiling. *J Pediatr Gastroenterol Nutr* 1984;3(4):545-50.
154. Kamm MA, Lennard-Jones JE, Thompson DG, Sobnack R, Garvie NW, Granowska M. Dynamic scanning defines a colonic defect in severe idiopathic constipation. *Gut* 1988;29(8):1085-92.
155. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. Prolonged multi-point recording of colonic manometry in the unprepared human colon:

providing insight into potentially relevant pressure wave parameters. *Am J Gastroenterol* 2001;96(6):1838-48.
156. Herve S, Savoye G, Behbahani A, Leroi AM, Denis P, Ducrotte P. Results of 24 h manometric recording of colonic motor activity with endoluminal instillation of bisacodyl in patients with severe chronic slow transit constipation. *Neurogastroenterol Motil* 2004;16:397-402.
157. Soffer EE, Scalabrini P, Wingate DL. Prolonged ambulant monitoring of human colonic motility. *Am J Physiol* 1989;257(4 Pt 1):G601-6.
158. Di Lorenzo C, Flores AF, Reddy SN, Snape WJ, Jr., Bazzocchi G, Hyman PE. Colonic manometry in children with chronic intestinal pseudo-obstruction. *Gut* 1993;34(6):803-7.
159. Narducci F, Bassotti G, Gaburri M, Morelli A. Twenty four hour manometric recording of colonic motor activity in healthy man. *Gut* 1987;28(1):17-25.
160. Kumar D, Williams NS, Waldron D, Wingate DL. Prolonged manometric recording of anorectal motor activity in ambulant human subjects: evidence of periodic activity. *Gut* 1989;30(7):1007-11.
161. Wright SH, Snape WJ, Jr., Battle W, Cohen S, London RL. Effect of dietary components on gastrocolonic response. *Am J Physiol* 1980;238(3):G228-32.
162. Kerlin P, Zinsmeister A, Phillips S. Motor responses to food of the ileum, proximal colon, and distal colon of healthy humans. *Gastroenterology* 1983;84(4):762-70.
163. Rao SS, Kavelock R, Beaty J, Ackerson K, Stumbo P. Effects of fat and carbohydrate meals on colonic motor response. *Gut* 2000;46(2):205-11.
164. Hagger R, Kumar D, Benson M, Grundy A. Colonic motor activity in slow-transit idiopathic constipation as identified by 24-h pancolonic ambulatory manometry. *Neurogastroenterol Motil* 2003;15(5):515-22.
165. Kaiser W. [Johann Gottlieb Kruger (1715-1759) and Christian Gottlieb Kratzenstein (1723-1795) as originators of modern electrotherapy]. *Zahn Mund Kieferheilkd Zentralbl* 1977;65(5):539-54.
166. Hirschmann JV. Benjamin Franklin and medicine. *Ann Intern Med* 2005;143(11):830-4.
167. Cule J. The contribution of John Wesley (1703-1791) to medical literature. *Hist Sci Med* 1982;17(Spec 1):328-31.
168. Parent A. Duchenne De Boulogne: a pioneer in neurology and medical photography. *Can J Neurol Sci* 2005;32(3):369-77.
169. Carroll D, Moore RA, McQuay HJ, Fairman F, Tramer M, Leijon G. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev* 2001(3):CD003222.
170. Chase J, Robertson VJ, Southwell B, Hutson J, Gibb S. Pilot study using transcutaneous electrical stimulation (interferential current) to treat chronic treatment-resistant constipation and soiling in children. *J Gastroenterol Hepatol* 2005;20(7):1054-61.
171. Bower WF, Yeung CK. A review of non-invasive electro neuromodulation as an intervention for non-neurogenic bladder dysfunction in children. *Neurourol Urodyn* 2004;23(1):63-7.
172. Ulett GA. Acupuncture--time for a second look. *South Med J* 1983;76(4):421-3.

173. Saletu B, Saletu M, Brown M, Stern J, Sletten I, Ulett G. Hypno-analgesia and acupuncture analgesia: a neurophysiological reality? *Neuropsychobiology* 1975;1(4):218-42.
174. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. *Trends Neurosci* 2003;26(1):17-22.
175. Kavia RB, Datta SN, Dasgupta R, Elneil S, Fowler CJ. Urinary retention in women: its causes and management. *BJU. Int* 2006;97(2):281-7.
176. Madersbacher H, Fischer J. Sacral anterior root stimulation: prerequisites and indications. *Neurourol Urodyn*. 1993;12(5):489-94.
177. Jarrett ME, Mowatt G, Glazener CM, Fraser C, Nicholls RJ, Grant AM, et al. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. *Br J Surg* 2004;91(12):1559-69.
178. Sheldon R, Kiff ES, Clarke A, Harris ML, Hamdy S. Sacral nerve stimulation reduces corticoanal excitability in patients with faecal incontinence. *Br J Surg* 2005;92(11):1423-31.
179. Leroi AM, Parc Y, Lehur PA, Mion F, Barth X, Rullier E, et al. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. *Ann Surg* 2005;242(5):662-9.
180. Robertson VJ, Low J, Reed A, Ward AR. Electrotherapy explained: Principles and prectice. *4th Edition* 2006.
181. Payne PA. Measurement of properties and function of skin. *Clinical Physics and Physiological Measurement* 1991;12(2):105-29.
182. Lerman BB, Deale OC. Relation between transcardiac and transthoracic current during defibrillation in humans. *Circ Res* 1990;67(6):1420-6.
183. Panescu D, Webster JG, Tompkins WJ, Stratbucker RA. Optimization of cardiac defibrillation by three-dimensional finite element modeling of the human thorax. *IEEE Trans Biomed Eng* 1995;42(2):185-92.
184. Waugaman WA. Prediction of internal electric current distribution from surface application in atrophied muscle tissue. *Biomed Sci Instrum* 2001;37:361-6.
185. Waugaman WA. Electrical current density model from surface electrodes. *Biomed Sci Instrum* 1997;34:131-6.
186. Waugaman WA. Verification of the finite element method to model subthreshold electrical current density in saline. *Biomed Sci Instrum* 1999;35:367-72.
187. Hartinger AE, Guardo R, Kokta V, Gagnon H. A 3-D hybrid finite element model to characterize the electrical behavior of cutaneous tissues. *IEEE Trans Biomed Eng*. 2010;57(4):780-9.
188. Iwamura Y, Uchino Y, Ozawa S, Kudo N. Excitatory and inhibitory components of somato-sympathetic reflex. *Brain Research* 1969;16(2):351-8.
189. Furgala A, Thor PJ, Kolasinska-Kloch W, Krygowska-Wajs A, Kopp B, Laskiewicz J. The effect of transcutaneous nerve stimulation (TENS) on gastric electrical activity. *J Physiol Pharmacol* 2001;52(4 Pt 1):603-10.
190. Chang FY, Chey WY, Ouyang A. Effect of transcutaneous nerve stimulation on esophageal function in normal subjects--evidence for a somatovisceral reflex. *Am J Chin Med* 1996;24(2):185-92.
191. Camilleri M, Malagelada JR, Kao PC, Zinsmeister AR. Effect of somatovisceral reflexes and selective dermatomal stimulation on postcibal antral pressure activity. *Am J Physiol* 1984;247(6 Pt 1):G703-8.

192. Guelrud M, Rossiter A, Souney PF, Mendoza S, Mujica V. The effect of transcutaneous nerve stimulation on sphincter of Oddi pressure in patients with biliary dyskinesia. *American Journal of Gastroenterology* 1991;86(5):581-5.
193. Guelrud M, Rossiter A, Souney PF, Sulbaran M. Transcutaneous electrical nerve stimulation decreases lower esophageal sphincter pressure in patients with achalasia. *Digestive Diseases & Sciences* 1991;36(8):1029-33.
194. Mearin F, Zacchi P, Armengol JR, Vilardell M, Malagelada JR. Effect of transcutaneous nerve stimulation on esophageal motility in patients with achalasia and scleroderma. *Scand J Gastroenterol* 1990;25(10):1018-23.
195. Rossi Z, Forlini G, Fenderico P, Cipolla R, Nasoni S. Electrogastrography. *Eur Rev Med Pharmacol Sci* 2005;9(5:1):29-35.
196. Chang CS, Chou JW, Ko CW, Wu CY, Chen GH. Cutaneous electrical stimulation of acupuncture points may enhance gastric myoelectrical regularity. *Digestion* 2002;66(2):106-11.
197. Lin X, Liang J, Ren J, Mu F, Zhang M, Chen JD. Electrical stimulation of acupuncture points enhances gastric myoelectrical activity in humans. *Am J Gastroenterol* 1997;92(9):1527-30.
198. Weinkauf JG, Yiannopoulos A, Faul JL. Transcutaneous electrical nerve stimulation for severe gastroparesis after lung transplantation. *J Heart Lung Transplant* 2005;24(9):1444.
199. Sylvester K, Kendall GP, Lennard-Jones JE. Treatment of functional abdominal pain by transcutaneous electrical nerve stimulation. *Br Med J (Clin Res Ed)* 1986;293(6545):481-2.
200. Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Digestive Diseases & Sciences* 1980;25(6):404-13.
201. Xiao WB, Liu YL. Rectal hypersensitivity reduced by acupoint TENS in patients with diarrhea-predominant irritable bowel syndrome: a pilot study. *Dig Dis Sci* 2004;49(2):312-9.
202. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. *Bjog* 2000;107(12):1460-70.
203. Vaizey CJ, Kamm MA, Turner IC, Nicholls RJ, Woloszko J. Effects of short term sacral nerve stimulation on anal and rectal function in patients with anal incontinence. *Gut* 1999;44(3):407-12.
204. Rosen HR, Urbarz C, Holzer B, Novi G, Schiessel R. Sacral nerve stimulation as a treatment for fecal incontinence. *Gastroenterology* 2001;121(3):536-41.
205. Malouf AJ, Vaizey CJ, Nicholls RJ, Kamm MA. Permanent sacral nerve stimulation for fecal incontinence. *Ann Surg* 2000;232(1):143-8.
206. Wilkins AJ, O'Callaghan MJ, Najman JM, Bor W, Williams GM, Shuttlewood G. Early childhood factors influencing health-related quality of life in adolescents at 13 years. *J Paediatr Child Health* 2004;40(3):102-9.
207. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. *Pharmacoeconomics* 1999;16(6):605-25.
208. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: The Child

Health Questionnaire in relation to the Health Utilities Index. *J Clin Epidemiol* 2002;55(1):67-76.
209. Schalock RL. The concept of quality of life: what we know and do not know. *J Intellect Disabil Res* 2004;48(Pt 3):203-16.
210. Davis E, Waters E, Mackinnon A, Reddihough D, Graham HK, Mehmet-Radji O, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Dev Med Child Neurol* 2006;48(4):311-8.
211. Gerharz EW, Eiser C, Woodhouse CR. Current approaches to assessing the quality of life in children and adolescents. *BJU Int* 2003;91(2):150-4.
212. Schmidt LJ, Garratt AM, Fitzpatrick R. Child/parent-assessed population health outcome measures: a structured review. *Child Care Health Dev* 2002;28(3):227-37.
213. Eiser C, Mohay H, Morse R. The measurement of quality of life in young children. *Child Care Health Dev* 2000;26(5):401-14.
214. De Civita M, Regier D, Alamgir AH, Anis AH, Fitzgerald MJ, Marra CA. Evaluating health-related quality-of-life studies in paediatric populations: some conceptual, methodological and developmental considerations and recent applications. *Pharmacoeconomics* 2005;23(7):659-85.
215. Howe ML, Courage ML. Independent paths in the development of infant learning and forgetting. *J Exp Child Psychol* 1997;67(2):131-63.
216. Flavell JH. Cognitive development: children's knowledge about the mind. *Annu Rev Psychol* 1999;50:21-45.
217. Goldman SL, Whitney-Saltiel D, Granger J, Rodin J. Children's representations of "everyday" aspects of health and illness. *J Pediatr Psychol* 1991;16(6):747-66.
218. Cremeens J, Eiser C, Blades M. A qualitative investigation of school-aged children's answers to items from a generic quality of life measure. *Child Care Health Dev* 2007;33(1):83-9.
219. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res* 2001;10(4):347-57.
220. Billson AL, Walker DA. Assessment of health status in survivors of cancer. *Arch Dis Child* 1994;70(3):200-4.
221. Phipps S, Dunavant M, Jayawardene D, Srivastiva DK. Assessment of health-related quality of life in acute in-patient settings: use of the BASES instrument in children undergoing bone marrow transplantation. *Int J Cancer Suppl* 1999;12:18-24.
222. Varni JW, Katz ER, Seid M, Quiggins DJ, Friedman-Bender A. The pediatric cancer quality of life inventory-32 (PCQL-32): I. Reliability and validity. *Cancer* 1998;82(6):1184-96.
223. Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. *Qual Life Res* 1998;7(5):387-97.
224. Czyzewski DI, Mariotto MJ, Bartholomew LK, LeCompte SH, Sockrider MM. Measurement of quality of well being in a child and adolescent cystic fibrosis population. *Med Care* 1994;32(9):965-72.

225. Eiser C, Havermans T, Craft A, Kernahan J. Development of a measure to assess the perceived illness experience after treatment for cancer. *Arch Dis Child* 1995;72(4):302-7.
226. Glaser AW, Davies K, Walker D, Brazier D. Influence of proxy respondents and mode of administration on health status assessment following central nervous system tumours in childhood. *Qual Life Res* 1997;6(1):43-53.
227. Pollock BH. Obstacles and opportunities for the use of health-related quality-of-life assessment in pediatric cancer clinical trials (discussion). *Int J Cancer Suppl* 1999;12:151-3.
228. Eiser C. Use of quality of life measures in clinical trials. *Ambul Pediatr* 2004;4(4 Suppl):395-9.
229. Brossart DF, Clay DL, Willson VL. Methodological and statistical considerations for threats to internal validity in pediatric outcome data: response shift in self-report outcomes. *J Pediatr Psychol* 2002;27(1):97-107.
230. Sprangers MA. Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials. *Cancer Treat Rev* 1996;22 Suppl A:55-62.
231. Reilly WT, Talley NJ, Pemberton JH, Zinsmeister AR. Validation of a questionnaire to assess fecal incontinence and associated risk factors: Fecal Incontinence Questionnaire. *Dis Colon Rectum* 2000;43(2):146-53; discussion 153-4.
232. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. *Dis Colon Rectum* 2000;43(1):9-16; discussion 16-7.
233. Trajanovska M, Catto-Smith AG. Quality of life measures for fecal incontinence and their use in children. *J Gastroenterol Hepatol* 2005;20(6):919-28.
234. Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. *Scand J Gastroenterol* 2005;40(5):540-51.
235. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;82(2):216-22.
236. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. *Dis Colon Rectum* 1999;42(12):1525-32.
237. Kwon S, Visco AG, Fitzgerald MP, Ye W, Whitehead WE. Validity and reliability of the Modified Manchester Health Questionnaire in assessing patients with fecal incontinence. *Dis Colon Rectum* 2005;48(2):323-31; discussion 331-4.
238. Ditesheim JA, Templeton JM, Jr. Short-term v long-term quality of life in children following repair of high imperforate anus. *J Pediatr Surg* 1987;22(7):581-7.
239. Frank L, Kleinman L, Farup C, Taylor L, Miner P, Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999;34(9):870-7.

240. Slappendel R, Simpson K, Dubois D, Keininger DL. Validation of the PAC-SYM questionnaire for opioid-induced constipation in patients with chronic low back pain. *European Journal of Pain: Ejp* 2006;10(3):209-17.
241. Bai Y, Yuan Z, Wang W, Zhao Y, Wang H. Quality of life for children with fecal incontinence after surgically corrected anorectal malformation. *J Pediatr Surg* 2000;35(3):462-4.
242. Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJ, Grootenhuis MA, Derkx BH, Benninga MA. Health related quality of life in disorders of defecation: the Defecation Disorder List. *Arch Dis Child* 2004;89(12):1124-7.
243. Rockwood TH. Incontinence severity and QOL scales for fecal incontinence. *Gastroenterology* 2004;126(1 Suppl 1):S106-13.
244. Landgraf JM, Maunsell E, Speechley KN, Bullinger M, Campbell S, Abetz L, et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. *Qual Life Res* 1998;7(5):433-45.
245. Starfield B, Riley AW, Green BF, Ensminger ME, Ryan SA, Kelleher K, et al. The adolescent child health and illness profile. A population-based measure of health. *Med Care* 1995;33(5):553-66.
246. Starfield B, Bergner M, Ensminger M, Riley A, Ryan S, Green B, et al. Adolescent health status measurement: development of the Child Health and Illness Profile. *Pediatrics* 1993;91(2):430-5.
247. Ravens-Sieberer U, Erhart M, Wille N, Wetzel R, Nickel J, Bullinger M. Generic health-related quality-of-life assessment in children and adolescents: methodological considerations. *Pharmacoeconomics* 2006;24(12):1199-220.
248. Rajmil L, Alonso J, Berra S, Ravens-Sieberer U, Gosch A, Simeoni MC, et al. Use of a children questionnaire of health-related quality of life (KIDSCREEN) as a measure of needs for health care services. *J Adolesc Health* 2006;38(5):511-8.
249. Ravens-Sieberer U, Gosch A, Rajmil L, Erhart M, Bruil J, Duer W, et al. KIDSCREEN-52 quality-of-life measure for children and adolescents. *Expert Review of Pharmacoeconomics & Outcomes Research* 2005;5(3):353-364.
250. Ravens-Sieberer U, Auquier P, Erhart M, Gosch A, Rajmil L, Bruil J, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. *Qual Life Res* 2007;16(8):1347-56.
251. Ravens-Sieberer U, Erhart M, Rajmil L, Herdman M, Auquier P, Bruil J, et al. Reliability, construct and criterion validity of the KIDSCREEN-10 score: a short measure for children and adolescents' well-being and health-related quality of life. *Qual Life Res* 2010;19(10):1487-500.
252. Wee HL, Lee WW, Ravens-Sieberer U, Erhart M, Li SC. Validation of the English version of the KINDL generic children's health-related quality of life instrument for an Asian population--results from a pilot test. *Qual Life Res* 2005;14(4):1193-200.
253. Vogels T, Verrips GH, Verloove-Vanhorick SP, Fekkes M, Kamphuis RP, Koopman HM, et al. Measuring health-related quality of life in children: the development of the TACQOL parent form. *Qual Life Res* 1998;7(5):457-65.
254. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care* 1999;37(2):126-39.

255. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;39(8):800-12.
256. Varni JW, Seid M, Knight TS, Uzark K, Szer IS. The PedsQL 4.0 Generic Core Scales: sensitivity, responsiveness, and impact on clinical decision-making. *J Behav Med* 2002;25(2):175-93.
257. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007;5:1.
258. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007;5:2.
259. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003;3(6):329-41.
260. Varni JW, Burwinkle TM. The PedsQL as a patient-reported outcome in children and adolescents with Attention-Deficit/Hyperactivity Disorder: a population-based study. *Health Qual Life Outcomes* 2006;4:26.
261. Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. *Jama* 2003;289(14):1813-9.
262. Tack J, van Outryve M, Beyens G, Kerstens R, Vandeplassche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut* 2009;58(3):457-65.
263. Meurette G, Lehur PA, Coron E, Regenet A. Long-term results of Malone's procedure with antegrade irrigation for severe chronic constipation. *Gastroenterol Clin Biol*. 2010;34(3):209-12.
264. Damon H, Dumas P, Mion H. Impact of anal incontinence and chronic constipation on quality of life. *Gastroenterol Clin Biol* 2004;28(1):16-20.
265. Asipu D, Jaffray B. Treatment of severe childhood constipation with restorative proctocolectomy. *Arch Dis Child* 2010;95(11):867-70.
266. Jiang CQ, Qian Q, Liu ZS, Bangoura G, Zheng KY, Wu YH. Subtotal colectomy with antiperistaltic cecoproctostomy for selected patients with slow transit constipation-from Chinese report. *Int J Colorectal Dis* 2008;23(12):1251-6.
267. Riss S, Herbst F, Birsoan T, Stift A. Postoperative course and long term follow up after colectomy for slow transit constipation--is surgery an appropriate approach? *Colorectal Dis* 2009;11(3):302-7.
268. Marchesi F, Sarli L, Percalli L, Sansebastiano GE, Veronesi L, Di Mauro D, et al. Subtotal colectomy with antiperistaltic cecorectal anastomosis in the treatment of slow-transit constipation: long-term impact on quality of life. *World J Surg* 2007;31(8):1858-64.
269. FitzHarris GP, Garcia-Aguilar J, Parker SC, Bullard KM, Madoff RD, Goldberg SM, et al. Quality of life after subtotal colectomy for slow-transit constipation: both quality and quantity count. *Dis Colon Rectum* 2003;46(4):433-40.

270. Markland AD, Greer WJ, Vogt A, Redden DT, Goode PS, Burgio KL, et al. Factors impacting quality of life in women with fecal incontinence. *Dis Colon Rectum* 2010;53(8):1148-54.
271. Templeton JM, Jr., Ditesheim JA. High imperforate anus--quantitative results of long-term fecal continence. *J Pediatr Surg* 1985;20(6):645-52.
272. Bongers M, Van Dijk M, Benninga M, Grootenhuis M. Health Related Quality of Life in Children with Constipation-Associated Fecal Incontinence. *J Paediatr* 2009;154:749-53.
273. Faleiros FT, Machado NC. Assessment of health-related quality of life in children with functional defecation disorders. *J Pediatr (Rio J)* 2006;82(6):421-5.
274. Starfield B, Riley AW, Green BF, Ensminger ME, S.A. R, Kelleher K, et al. The adolescent child health and illness profile. A population-based measure of health. *Med Care* 1995;33(5):553-66.
275. Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx BH. Quality of life in paediatric inflammatory bowel disease measured by a generic and a disease-specific questionnaire. *Acta Paediatr* 2002;91(3):348-54.
276. Poley MJ, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJ. Short term and long term health related quality of life after congenital anorectal malformations and congenital diaphragmatic hernia. *Arch Dis Child* 2004;89(9):836-41.
277. Youssef NN, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic childhood constipation is associated with impaired quality of life: a case-controlled study. *J Pediatr Gastroenterol Nutr* 2005;41(1):56-60.
278. Clarke MC, Chow CS, Chase JW, Gibb S, Hutson JM, Southwell BR. Quality of life in children with slow transit constipation. *J Pediatr Surg* 2008;43(2):320-4.
279. Sutcliffe JR, King SK, Southwell BR, Hutson JM. Paediatric constipation for adult surgeons--article 1: targeting the cause. *ANZ J Surg* 2004;74(9):777-80.
280. Hutson JM, McNamara J, Gibb S, Shin YM. Slow transit constipation in children. *J Paediatr Child Health* 2001;37(5):426-30.
281. Wald A. Slow Transit Constipation. *Curr Treat Options Gastroenterol* 2002;5(4):279-283.
282. Porter AJ, Wattchow DA, Hunter A, Costa M. Abnormalities of nerve fibers in the circular muscle of patients with slow transit constipation. *Int J Colorectal Dis* 1998;13(5-6):208-16.
283. El-Salhy M, Norrgard O, Spinnell S. Abnormal colonic endocrine cells in patients with chronic idiopathic slow-transit constipation. *Scand J Gastroenterol* 1999;34(10):1007-11.
284. Sinha I, Jones L, Smyth RL, Williamson PR. A systematic review of studies that aim to determine which outcomes to measure in clinical trials in children. *PLoS Med* 2008;5(4):e96.
285. McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, Davidson K, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain* 2008;9(9):771-83.

286. Ramsey BW, Boat TF. Outcome measures for clinical trials in cystic fibrosis. Summary of a Cystic Fibrosis Foundation consensus conference. *J Paediatr* 1994;124(2):177-92.
287. Sanders C, Egger M, Donovan J, Tallon D, Frankel S. Reporting on quality of life in randomised controlled trials: bibliographic study. *BMJ* 1998;317:1191-4.
288. Brundage M, Bass B, Davidson J, Queenan J, Bezjak A, Ringash J, et al. Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. *Qual Life Res* 2010;Eprint(Nov 26th).
289. Drossman DA. The functional gastrointestinal disorders and the Rome II process. *Gut* 1999;45 Suppl 2:II1-5.
290. Rasquin A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla P, et al. Childhood functional gastrointestinal disorders. *Gut* 1999;45(Suppl 2):1160-8.
291. Perrin EC, Newacheck P, Pless IB, Drotar D, Gortmaker SL, Leventhal J, et al. Issues Involved in the Definition and Classification of Chronic Health Conditions. *Pediatrics* 1993;91(4):787-93.
292. Williams J, Wake M, Hesketh K, Maher E, Waters E. Health-related quality of life of overweight and obese children. *Jama* 2005;293(1):70-6.
293. Clarke MC, Chase J, Gibb S, Catto-Smith AG, Hutson J, Southwell B. Standard medical therapies do not alter colonic transit time in children with treatment-resistant slow-transit constipation. *Pediatr Surg Int* 2009;25(6):473-8.
294. Ripetti V, Caputo D, Greco S, Alloni R, Coppola R. Is total colectomy the right choice in intractable slow-transit constipation? *Surgery* 2006;140(3):435-40.
295. Zutshi M, Hull TL, Trzcinski R, Arvelakis A, Xu M. Surgery for slow transit constipation: are we helping patients? *Int J Colorectal Dis* 2007;22(3):265-9.
296. Sarli L, Iusco D, Donadei E, Costi R, Sgobba G, Violi V, et al. The rationale for cecorectal anastomosis for slow transit constipation. *Acta Biomed* 2003;74 Suppl 2:74-9.
297. Notghi A, Hutchinson R, Kumar D, Smith NB, Harding LK. Simplified method for the measurement of segmental colonic transit time. *Gut* 1994;35(7):976-81.
298. Masoomi MA, Britten AJ, Kumar D, Joseph AE. Inter-observer reproducibility of quantitative radionuclide colonic transit imaging. *Nucl Med Commun* 1999;20(6):547-50.
299. Hutson JM, Catto-Smith T, Gibb S, Chase J, Shin YM, Stanton M, et al. Chronic constipation: no longer stuck! Characterization of colonic dysmotility as a new disorder in children. *J Pediatr Surg* 2004;39(6):795-9.
300. Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. *Gut* 1996;39(2):299-305.
301. von der Ohe MR, Camilleri M. Measurement of small bowel and colonic transit: indications and methods. *Mayo Clin Proc* 1992;67(12):1169-79.
302. Lundin E, Graf W, Garske U, Nilsson S, Maripuu E, Karlbom U. Segmental colonic transit studies: comparison of a radiological and a scintigraphic method. *Colorectal Dis* 2007;9(4):344-51.

303. Abrahamsson H, Antov S, Bosaeus I. Gastrointestinal and colonic segmental transit time evaluated by a single abdominal x-ray in healthy subjects and constipated patients. *Scand J Gastroenterol Suppl* 1988;152:72-80.
304. Stivland T, Camilleri M, Vassallo M, Proano M, Rath D, Brown M, et al. Scintigraphic measurement of regional gut transit in idiopathic constipation. *Gastroenterology* 1991;101(1):107-15.
305. Clarke MC, Chase J, Gibb S, Hutson J, Southwell B. Improvement of quality of life in children with slow transit constipation after treatment with transcutaneous electrical stimulation. *J Pediatr Surg* 2009;44(6):1268-72.
306. Clarke MC, Chase J, Gibb S, Robertson VJ, Catto-Smith AG, Hutson J, et al. Decreased colonic transit time after transcutaneous interferential electrical stimulation in children with slow transit constipation. *J Pediatr Surg* 2009;44(2):408-12.
307. Kajbafzadeh AM, Sharifi-Rad L, Baradaran N, Nejat F. Effect of pelvic floor interferential electrostimulation on urodynamic parameters and incontinency of children with myelomeningocele and detrusor overactivity. *Urology* 2009;74(2):324-9.
308. Laycock J, Green R. Does pre-modulated interferential therapy cure genuine stress incontinence? *Physiotherapy* 1993;798(8):553-561.
309. Emmerson C. A preliminary study of the effect of interferential therapy on detrusor instability in patients with multiple sclerosis. *Aust J Physiother* 1987;33(1):64-5.
310. Holschneider AM. Treatment and functional results of anorectal continence in children with imperforate anus. *Acta Chir Belg* 1983;82(3):191-204.
311. Fishman L, Lenders C, Fortunato C, Noonan C, Nurko S. Increased prevalence of constipation and fecal soiling in a population of obese children. *J Pediatr* 2004;145(2):253-4.
312. Booth ML, Chey T, Wake M, Norton K, Hesketh K, Dollman J, et al. Change in the prevalence of overweight and obesity among young Australians, 1969-1997. *Am J Clin Nutr* 2003;77(1):29-36.
313. Goligher JC, Hughes ES. Sensibility of the rectum and colon. Its role in the mechanism of anal continence. *Lancet* 1951;1(6654):543-7.
314. Corman ML. Colon and Rectal Surgery. *Lippincott, Williams & Wilkins* 2005.
315. Keighley MR, Winslet MC, Yoshioka K, Lightwood R. Discrimination is not impaired by excision of the anal transition zone after restorative proctocolectomy. *Br J Surg* 1987;74(12):1118-21.
316. Read MG, Read NW. Role of anorectal sensation in preserving continence. *Gut* 1982;23(4):345-7.
317. Loening-Baucke VA. Abnormal rectoanal function in children recovered from chronic constipation and encopresis. *Gastroenterology* 1984;87(6):1299-304.
318. Caldwell KP. The electrical control of sphincter incompetence. *Lancet* 1963;2(7300):174-5.
319. Glen ES. Intra-anal electrode: a stimulus to bowel and bladder control. *J Pediatr Surg* 1971;6(2):138-42.
320. Glen ES. Effective and safe control of incontinence by the intra-anal plug electrode. *Br J Surg* 1971;58(4):249-52.
321. Brindley GS. An implant to empty the bladder or close the urethra. *J Neurol Neurosurg Psychiatry* 1977;40(4):358-69.

322. Brindley GS, Polkey CE, Rushton DN. Sacral anterior root stimulators for bladder control in paraplegia. *Paraplegia* 1982;20(6):365-81.
323. Opsomer RJ, Klarskov P, Holm-Bentzen M, Hald T. Long term results of superselective sacral nerve resection for motor urge incontinence. *Scand J Urol Nephrol* 1984;18(2):101-5.
324. Dinning PG, Fuentealba SE, Kennedy ML, Lubowski DZ, Cook IJ. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation. *Colorectal Dis* 2007;9(2):123-32.
325. Kenefick NJ. Sacral nerve neuromodulation for the treatment of lower bowel motility disorders. *Ann R Coll Surg Engl* 2006;88(7):617-23.
326. Kenefick NJ, Vaizey CJ, Cohen CR, Nicholls RJ, Kamm MA. Double-blind placebo-controlled crossover study of sacral nerve stimulation for idiopathic constipation. *Br J Surg* 2002;89(12):1570-1.
327. Braun PM, Baezner H, Seif C, Boehler G, Bross S, Eschenfelder CC, et al. Alterations of cortical electrical activity in patients with sacral neuromodulator. *Eur Urol* 2002;41(5):562-6; discussion 566-7.
328. Bower WF. Neuromodulation as an adjunct to intervention for voiding dysfunction in children. *Dialogues in pediatric urology* 2002;25(8):5-7.
329. Mowatt G, Glazener C, Jarrett M. Sacral nerve stimulation for fecal incontinence and constipation in adults: a short version Cochrane review. *Neurourol Urodyn* 2008;27(3):155-61.
330. Vaizey CJ, Kamm MA, Roy AJ, Nicholls RJ. Double-blind crossover study of sacral nerve stimulation for fecal incontinence. *Dis Colon Rectum* 2000;43(3):298-302.
331. Belsey J, Greenfield S, Candy D, Geraints M. Systematic review: impact of constipation on quality of life in adults and children. *Ailment Pharmacol Ther* 201o;31(9):938-949.
332. Wald A, Sigurdsson L. Quality of life in children and adults with constipation. *Best Pract Res Clin Gastroenterol* 2011;25(1):29-41.
333. Piccirillo MF, Reissman P, Wexner SD. Colectomy as treatment for constipation in selected patients. *Br J Surg* 1995;82(7):898-901.
334. Levitt M, Mathis K, Pemberton J. Surgical treatment for constipation in children and adults. *Best Pract Res Clin Gastroenterol* 2011;25:167-179.
335. Lander J, Fowler-Kerry S. TENS for children's procedural pain. *Pain* 1993;52(2):209-16.
336. Merkel SI, Gutstein HB, Malviya S. Use of transcutaneous electrical nerve stimulation in a young child with pain from open perineal lesions. *J Pain Symptom Manage* 1999;18(5):376-81.
337. Wang WC, George SL, Wilimas JA. Transcutaneous electrical nerve stimulation treatment of sickle cell pain crises. *Acta Haematol* 1988;80(2):99-102.
338. Ward A. Electrical stimulation using kilohertz-frequency alternating current. *Phys Ther* 2009;89(2):181-90.
339. Ismail KA, Chase J, Gibb S, Clarke MC, Catto-Smith AG, Robertson VJ, et al. Daily transabdominal electrical stimulation at home increased defecation in children with slow-transit constipation: a pilot study. *J Paediatr Surg* 2009;44:2388-92.

Appendices

Appendix 1 - Fecal Incontinence Questionnaire [231]

Have you had problems with leakage of stool (accidents or soiling because of the inability to control the passage of stool) until you reached a toilet? (Check answer.)

[] No
[] Yes

IN THE LAST YEAR, did you have to take medication (like antidiarrheals, Lomotil, Imodium AD, etc.) to prevent leakage of stool? (Check one answer.)

[] No
[] Yes, sometimes (less than 25% of the time)
[] Yes, often (more than 25% of the time)
[] Yes, usually (more than 75% of the time)

If YES, what did you take?

When in your life did this problem with leakage of stool FIRST begin as close as you can recall? (Check one answer.)

[] in the last 6 months
[] 7 months to 1 year ago
[] more than 1 year to 2 years ago
[] more than 2 years to 5 years ago
[] more than 5 years to 10 years ago
[] more than 10 years to 20 years ago
[] more than 20 years ago

IN THE LAST YEAR, did you *ever* wear a pad to protect your underclothes from soilage or leakage of stool? (Check one answer.)

[] never
[] sometimes (less than 25% of the time)
[] often (more than 25% of the time)
[] usually (more than 75% of the time)

If you have to wear a pad to protect your underwear from stool leakage, when do you wear it? (Check one answer.)

[] while awake
[] while asleep
[] both while awake and asleep
[] I do not wear a pad

IN THE LAST YEAR, when was the leakage of stool MOST frequent? (Check one answer.)

[] while awake
[] while asleep
[] there was no difference in leakage while asleep or awake

IN THE LAST YEAR, have you felt the need to always know where the nearest toilet is? (Check one answer.)

[] No
[] Yes

When leakage of stool has occurred IN THE LAST YEAR, did you have problems with leakage of LIQUID or RUNNY stool? (Check one answer.)

[] never
[] sometimes (less than 25% of the time that leakage occurred)
[] often (more than 25% of the time that leakage occurred)
[] usually (more than 75% of the time that leakage occurred)

When leakage of stool has occurred IN THE LAST YEAR, did you have problems with leakage of SOLID, or formed stool? (Check one answer.)

[] never
[] sometimes (less than 25% of the time that leakage occurred)
[] often (more than 25% of the time that leakage occurred)
[] usually (more than 75% of the time that leakage occurred)

When these "accidents" with leakage of stool occurred IN THE LAST YEAR, how much stool TYPICALLY leaked out? (Check one answer.)

[] a small amount, with a stain about the size of a quarter
[] moderate amounts (often requiring a change of pad or underwear)
[] large bowel movements (often requiring a complete change of clothes)
[] solid or formed stool

IN THE LAST YEAR, have you been able to tell when this leakage of stool was about to occur? (Check one answer.)

[] never
[] sometimes (less than 25% of the time)
[] often (more than 25% of the time)
[] usually (more than 75% of the time)

When these "accidents" with leakage of stool occurred, were you aware when the leakage was *actually happening?* (Check one answer.)

[] never
[] sometimes (less than 25% of the time)
[] often (more than 25% of the time)
[] usually (more than 75% of the time)

Have you had difficulty telling the difference between the need to pass gas and the need to pass stool IN THE LAST YEAR? (Check one answer.)

[] never
[] sometimes (less than 25% of the time)
[] often (more than 25% of the time)
[] usually (more than 75% of the time)

Appendix 2 - Fecal Incontinence Quality of Life Scale [232]

Q 1: In general, would you say your health is:

1 [] Excellent
2 [] Very Good
3 [] Good
4 [] Fair
5 [] Poor

Q2: For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage. (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, (N/A).)

1 = Most of the time
2 = Some of the time
3 = A little of the time
4 = None of the time

Due to accidental bowel leakage:

a. I am afraid to go out
1 2 3 4 N/A
b. I avoid visiting friends
1 2 3 4 N/A
c I avoid staying overnight away from home
1 2 3 4 N/A
d. It is difficult for me to get out and do things like going to a movie or to church
1 2 3 4 N/A
e. I cut down on how much I eat before I go out
1 2 3 4 N/A
f. Whenever I am away from home, I try to stay near a restroom as much as possible
1 2 3 4 N/A
g It is important to plan my schedule (daily activities) around my bowel pattern
1 2 3 4 N/A
h. I avoid traveling
1 2 3 4 N/A
i I worry about not being able to get to the toilet in time
1 2 3 4 N/A
j. I feel I have no control over my bowels
1 2 3 4 N/A
k. I can't hold my bowel movement long enough to get to the bathroom
1 2 3 4 N/A
l. I leak stool without even knowing it
1 2 3 4 N/A
m. I try to prevent bowel accidents by staying very near a bathroom
1 2 3 4 N/A

Q3: Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items. (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, N/A).

1 = Strongly agree
2 = Somewhat agree
3 = Somewhat disagree
4 = Strongly disagree

Due to accidental bowel leakage:

a. I feel ashamed
1 2 3 4 N/A

b. I can not do many of things I want to do
1 2 3 4 N/A

c. I worry about bowel accidents
1 2 3 4 N/A

d. I feel depressed
1 2 3 4 N/A

e. I worry about others smelling stool on me
1 2 3 4 N/A

f. I feel like I am not a healthy person
1 2 3 4 N/A

g. I enjoy life less
1 2 3 4 N/A

h. I have sex less often than I would like to
1 2 3 4 N/A

i. I feel different from other people
1 2 3 4 N/A

j. The possibility of bowel accidents is always on my mind
1 2 3 4 N/A

k. I am afraid to have sex
1 2 3 4 N/A

1. I avoid traveling by plane or train
1 2 3 4 N/A

m. I avoid going out to eat
1 2 3 4 N/A

n. Whenever I go someplace new, I specifically locate where the bathrooms are
1 2 3 4 N/A

Q 4: During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?

1 [] Extremely So - To the point that I have just about given up
2 [] Very Much So
3 [] Quite a Bit
4 [] Some - Enough to bother me
5 [] A Little Bit
6 [] Not At All

Scale Scoring

Scales range from 1 to 5, with a 1 indicating a lower functional status of quality of life. Scale scores are the **average** (mean) response to **all** items in the scale *(e.g.,* add the responses to **all** questions in a scale together and then divide by the number of items in the **scale.** Not Apply is coded as a missing value in the analysis for **all** questions.)

Scale 1. Lifestyle, ten items: Q2a Q2b Q2c Q2d Q2e Q2g Q2h Q3b Q31 Q3m
Scale 2. Coping/Behavior, nine items: Q2f Q2i Q2j Q2k Q2m Q3d Q3h Q3j Q3n
Scale 3. Depression/Self Perception, seven items: Q1 Q3d Q3f Q3g Q3i Q3k Q4, (Question 1 is reverse coded.)
Scale 4. Embarrassment, three items: Q21 Q3a Q3e

Appendix 3 - Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL) [234]

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

The following questions ask about your symptoms related to constipation.

During the past 2 weeks, to what extent or intensity have you . . .

1 = Not at all
2 = A little bit
3 = Moderately
4 = Quite a bit
5 = Extremely

1. Felt bloated to the point of bursting?
   1 2 3 4 5
2. Felt heavy because of your constipation?
   1 2 3 4 5

The next few questions ask about how constipation affects your daily life.

During the past 2 weeks, how much of the time have you . . .

1 = None of the time
2 = A little of the time
3 = Some of the time
4 = Most of the time
5 = All of the time

3. Felt any physical discomfort?
   1 2 3 4 5
4. Felt the need to have a bowel movement but not been able to?
   1 2 3 4 5
5. Been embarrassed to be with other people?
   1 2 3 4 5
6. Been eating less and less because of not being able to have bowel movements?
   1 2 3 4 5

The next few questions ask about how constipation affects your daily life.

During the past 2 weeks, to what extent or intensity have you . . .

1 = Not at all
2 = A little bit
3 = Moderately
4 = Quite a bit
5 = Extremely

7. Had to be careful about what you eat?
1 2 3 4 5
8. Had a decreased appetite?
1 2 3 4 5
9. Been worried about not being able to choose what you eat (for example, at a friend's house)?
1 2 3 4 5
10. Been embarrassed about staying in the bathroom for so long when you were away from home?
1 2 3 4 5
11. Been embarrassed about having to go to the bathroom so often when you were away from home?
1 2 3 4 5
12. Been worried about having to change your daily routine (for example, traveling, being away from home)?
1 2 3 4 5

The next few questions ask about your feelings related to constipation.

During the past 2 weeks, how much of the time have you . . .

1 = None of the time
2 = A little of the time
3 = Some of the time
4 = Most of the time
5 = All of the time

13. Felt irritable because of your condition?
1 2 3 4 5
14. Been upset by your condition?
1 2 3 4 5
15. Felt obsessed by your condition?
1 2 3 4 5
16. Felt stressed by your condition?
1 2 3 4 5

17. Felt less self-confident because of your condition?

1 2 3 4 5

18. Felt in control of your situation?

1 2 3 4 5

The next questions ask about your feelings related to constipation.

During the past 2 weeks, to what extent or intensity have you . . .

1 = Not at all
2 = A little bit
3 = Moderately
4 = Quite a bit
5 = Extremely

19. Been worried about not knowing when you are going to be able to have a bowel movement?

1 2 3 4 5

20. Been worried about not being able to have a bowel movement?

1 2 3 4 5

21. Been increasingly bothered by not being able to have a bowel movement?

1 2 3 4 5

The next questions ask about your life with constipation.

During the past 2 weeks, how much of the time have you . . .

1 = None of the time
2 = A little of the time
3 = Some of the time
4 = Most of the time
5 = All of the time

22. Been worried that your condition will get worse?

1 2 3 4 5

23. Felt that your body was not working properly?

1 2 3 4 5

24. Had fewer bowel movements than you would like?

1 2 3 4 5

The next questions ask about your degree of satisfaction related to constipation.

During the past 2 weeks, to what extent or intensity have you been . . .

1 = Not at all
2 = A little bit
3 = Moderately
4 = Quite a bit
5 = Extremely

25. Satisfied with how often you have a bowel movement?
1 2 3 4 5
26. Satisfied with the regularity of your bowel movements?
1 2 3 4 5
27. Satisfied with the time it takes for food to pass through the intestines?
1 2 3 4 5
28. Satisfied with your treatment?
1 2 3 4 5

Appendix 4 - The Gastrointestinal Quality of Life Index (GIQLI) [235]

1. How often during the past 2 weeks have you had pain in the abdomen?

all of the time, most of the time, some of the time, a little of the time, never

2. How often during the past 2 weeks have you had a feeling of fullness in the upper abdomen?

all of the time, most of the time, some of the time, a little of the time, never

3. How often during the past 2 weeks have you had bloating (sensation of too much gas in the abdomen)?

all of the time, most of the time, some of the time, a little of the time, never

4. How often during the past 2 weeks have you been troubled by excessive passage of gas through the anus?

all of the time, most of the time, some of the time, a little of the time, never

5. How often during the past 2 weeks have you been troubled by strong burping or belching?

all of the time, most of the time, some of the time, a little of the time, never

6. How often during the past 2 weeks have you been troubled by gurgling noises from the abdomen?

all of the time, most of the time, some of the time, a little of the time, never

7. How often during the past 2 weeks have you been troubled by frequent bowel movements?

all of the time, most of the time, some of the time, a little of the time, never

8. How often during the past 2 weeks have you found eating to be a pleasure?

all of the time, most of the time, some of the time, a little of the time, never

9. Because of your illness, to what extent have you restricted the kinds of food you eat?

very much, much, somewhat, a little, not at all

10. During the past 2 weeks, how well have you been able to cope with everyday stresses?

extremely poorly, poorly, moderately, well, extremely well

11. How often during the past 2 weeks have you been sad about being ill?

all of the time, most of the time, some of the time, a little of the time, never

12. How often during the past 2 weeks have you been nervous or anxious about your illness?

all of the time, most of the time, some of the time, a little of the time, never

13. How often during the past 2 weeks have you been happy with life in general?

never, a little of the time, some of the time, most of the time, all of the time

14. How often during the past 2 weeks have you been frustrated about your illness?

all of the time, most of the time, some of the time, a little of the time, never

15. How often during the past 12 weeks have you been tired or fatigued?

all of the time, most of the time, some of the time, a little of the time, never

16. How often during the past 2 weeks have you felt unwell?

all of the time, most of the time, some of the time, a little of the time, never

17. Over the past week, have you woken up in the night?

every night, 5-6 nights, 3-4 nights, 1-2 nights, never

18. Since becoming ill, have you been troubled by changes in your appearance?

a great deal, a moderate amount, somewhat, a little bit, not at all

19. Because of your illness, how much physical strength have you lost?

a great deal, a moderate amount, some, a little bit, none

20. Because of your illness, to what extent have you lost your endurance?

a great deal, a moderate amount, somewhat, a little bit, not at all

21. Because of your illness, to what extent do you feel unfit?

extremely unfit, moderately unfit, somewhat unfit, a little unfit, fit

22. During the past 2 weeks, how often have you been able to complete your normal daily activities (school, work, household)?

all of the time, most of the time, some of the time, a little of the time, never

23. During the past 2 weeks, how often have you been able to take part in your usual patterns of leisure or recreational activities?

all of the time, most of the time, some of the time, a little of the time, never

24. During the past 2 weeks, how much have you been troubled by the medical treatment of your illness?

very much, much, somewhat, a little, not at all

25. To what extent have your personal relations with people close to you (family or friends) worsened because of your illness?

very much, much, somewhat, a little, not at all

26. To what extent has your sexual life been impaired (harmed) because of your illness?

very much, much, somewhat, a little, not at all

27. How often during the past 2 weeks, have you been troubled by fluid or food coming up into your mouth (regurgitation)?

all of the time, most of the time, some of the time, a little of the time, never

28. How often during the past 2 weeks have you felt uncomfortable because of your slow speed of eating?

all of the time, most of the time, some of the time, a little of the time, never

29. How often during the past 2 weeks have you had trouble swallowing your food?

all of the time, most of the time, some of the time, a little of the time, never

30. How often during the past 2 weeks have you been troubled by urgent bowel movements?

all of the time, most of the time, some of the time, a little of the time, never

31. How often during the past 2 weeks have you been troubled by diarrhoea?

all of the time, most of the time, some of the time, a little of the time, never

32. How often during the past 2 weeks have you been troubled by constipation?

all of the time, most of the time, some of the time, a little of the time, never

33. How often during the past 2 weeks have you been troubled by nausea?

all of the time, most of the time, some of the time, a little of the time, never

34. How often during the past 2 weeks have you been troubled by blood in the stool?

all of the time, most of the time, some of the time, a little of the time, never

35. How often during the past 2 weeks have you been troubled by heartburn?

all of the time, most of the time, some of the time, a little of the time, never

36. How often during the past 2 weeks have you been troubled by uncontrolled stools?

all of the time, most of the time, some of the time, a little of the time, never

Calculation of the score:

most desirable option: 4 points

least desirable option: 0 points

GIQLI score: sum of the points

Appendix 5 - Modified Manchester Health Questionnaire [237]

SECTION A&B

1 = Never	a = Never
2 = Rarely	b = 1 to 3 times a month
3 = Sometimes	c = Once a week
4 = Often	d = 2 or more times a week
5 = Always	e = Once a day
	f = 2 or more times a day

A1. How often do you have a strong desire to move your bowels which makes you rush to the toilet?

1 2 3 4 5

A2. How often in the past month have you experienced any amount of accidental bowel leakage that consisted of solid stool?

a b c d e f

B1. Do you lose any solid stool when coughing or sneezing?

1 2 3 4 5

B2. Do you lose any solid stool when walking?

1 2 3 4 5

B3. Besides coughing, sneezing, and walking, do you lose any solid stool during the rest of the day or night?

1 2 3 4 5

A3. How often in the past month have you experienced any amount of accidental bowel leakage that consisted of liquid stool?

a b c d e f

B4. When you leak stool, how often is it liquid or watery?

1 2 3 4 5

B5. Do you lose any liquid stool when coughing or sneezing?

1 2 3 4 5

B6. Do you lose any liquid stool when walking?

1 2 3 4 5

B7. Besides coughing, sneezing, and walking, do you lose any liquid stool during the rest of the day or night?

1 2 3 4 5

A4. How often in the past month have you experienced any amount of accidental bowel leakage that consisted of mucus?

a b c d e f

A5. How often in the past month have you experienced any amount of accidental bowel leakage that consisted of gas?

a b c d e f

B8. Do you lose any gas when coughing or sneezing?

1 2 3 4 5

B9. Do you lose any gas when walking?

1 2 3 4 5

B10. Besides coughing, sneezing, and walking, do you lose any gas during the rest of the day or night?

1 2 3 4 5

B11. Do you have difficulty controlling gas?

1 2 3 4 5

SECTION C: <u>If the answers to A1, A2, A3, A4, and A5 are all "Never," skip this section.</u>

A = 1-2 times a day
B = 3-4 times a day
C = 5-6 times a day
D = 7 or more times a day
E = every other day
F = less than every other day

6 = 0
7 = 25%
8 = 50%
9 = 75%
10 = 100%

C1. How much do you think your bowel problem affects your life?

1 2 3 4 5

C2. How often do you move your bowels each day?

A B C D E F

C3. Do you have difficulty wiping clean after you have moved your bowels?

1 2 3 4 5

C4. What percent of your bowel movements are hard or little balls?

6 7 8 9 10

C5. What percent of your bowel movements are loose or watery?

6 7 8 9 10

Role limitations:

C6. Do you have a problem with your bowels that affects doing jobs within the home?

1 2 3 4 5

C6a. If so, how often does it affect you?

1 2 3 4 5

C7. Do you have a problem with your bowels that affects your job, or your normal daily activities outside the home?

1 2 3 4 5

C7a. If so, how often does it affect you?

1 2 3 4 5

Physical/social limitations:

C8. Do you have a problem with your bowels that affects your ability to travel?

1 2 3 4 5

C8a. If so, how often does it affect you?

1 2 3 4 5

C9. Do you have a problem with your bowels that affects your physical activities (such as going for a walk, running, sport, gym, etc.)?

1 2 3 4 5

C9a. If so, how often does it affect you?

1 2 3 4 5

C10. Do you have a problem with your bowels that limits your social life?

1 2 3 4 5

C10a. If so, how often, does it affect you?

1 2 3 4 5

C11. Do you have a problem with your bowels that limits your ability to see and visit friends?

1 2 3 4 5

C11a. If so, how often does it affect you?

1 2 3 4 5

Personal relationships:

C12. Do you have a problem with your bowels that affects your relationship with your partner?

1 2 3 4 5

C12a. If yes, how often does it affect your relationship?

1 2 3 4 5

C13. Do you have a problem with your bowels that affects your family life?

1 2 3 4 5

C13a. If so, how often does it affect your family life?

1 2 3 4 5

Emotions:

C14. Do you have a problem with your bowels that makes you feel depressed?

1 2 3 4 5

C14a. If yes, how often does it affect you?

1 2 3 4 5

C15. Do you have a problem with your bowels that makes you feel anxious or nervous?

1 2 3 4 5

C15a. If yes, how often does it affect you?

1 2 3 4 5

C16. Do you have a problem with your bowels that makes you feel bad about yourself?

1 2 3 4 5

C16a. If yes, how often does it affect you?

1 2 3 4 5

Sleep/energy:

C17. Do you have a problem with your bowels that affects your sleep?

1 2 3 4 5

C17a. If so, how often does it affect your sleep?

1 2 3 4 5

C18. Do you have a problem with your bowels that makes you feel worn out and tired?

1 2 3 4 5

C18a. If yes, how often does it affect you?

1 2 3 4 5

Sexual Activity: (For general audience, skip questions C19a to C19c.)

C19. Have you resumed sexual activity since delivery?

C19a. If "Yes," when did you resume sexual activity? __ __ weeks after delivery

C19b. If "No," why have you not resumed sexual activity? (and skip to C24)

1 = not allowed by clinician yet
2 = too tired
3 = too painful
8 = other; specify_____

C20. Do you have a problem with your bowels that affects your sex life?

1 2 3 4 5

C20a. If so, how often does it affect your sex life?

1 2 3 4 5

C21. Do you lose any gas during or after sexual activity?

1 2 3 4 5

C22. Do you lose any stool during or after sexual activity?

1 2 3 4 5

C23. Do you lose any urine during or after sexual activity?

1 2 3 4 5

Lifestyle Adaptation:

C24. Do you wear pads to keep clean because of a problem with your bowels?

1 2 3 4 5

C24a. If yes, how often do you wear pads?

1 2 3 4 5

C25. Are you careful about how much food you eat because of a problem with your bowels?

1 2 3 4 5

C25a. If yes, how often are you careful about how much food you eat?

1 2 3 4 5

C26. Do you change your underclothes because they get dirty due to a problem with your bowels?

1 2 3 4 5

C26a. If yes, how often do you change your underclothes for this reason?

1 2 3 4 5

C27. Do you worry about odor because of a problem with your bowels?

1 2 3 4 5

C27a. If yes, how often do you worry about it?

1 2 3 4 5

C28. Do you get embarrassed because of a problem with your bowels?

1 2 3 4 5

C28a. If yes, how often do you get embarrassed?

1 2 3 4 5

Medical:

C29. Did you bring any of your bowel symptoms to the attention of your clinician?

1 2 3 4 5

C30. Have you received treatment for your bowel symptoms?

C30a. If "Yes," please specify:

a = medical
b = behavioral
c = pelvic muscle exercise
d = surgical (specify)_____
e = other (specify)_____

C31. Do you have any comments that are important to you which have not been covered?

A2, A3, A4, and A5 compose the FISI component of the questionnaire.

Appendix 6 - Ditesheim and Templeton QoL scoring system [271]

Regular school attendance	Full time Part time Never	1.0 0.5 0
Social relations	No limitations Some self-imposed or parental restrictions (eg, no overnights, no camping) Very limited or restricted (eg, no parties, no dating, very little contact with peers)	1.0 0.5 0
Physical capabilities	Toilet free (able to be at least one hour away from a toilet, as on a long-distance car ride) Participates in any sport; no limits on swimming (age dependent) No job limitations (age dependent)	0.5 0.5 0.5
Total score	(range)	0-3.5

Appendix 7 - Patient Assessment of Constipation Symptoms (PAC-SYM) [240]

"How severe have each of these symptoms been in the last two weeks?"

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, like you did not "finish".
9. Bowel movements that were too hard.
10. Bowel movements that were too small.
11. Straining or squeezing to try to pass bowel movements.
12. Feeling like you had to pass a bowel movement but you could not ("false alarm").

Items are rated on a 5-point (0–4) Likert scale.

Responses are scored as 0 = absence of symptom, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.

The ABD, REC and STO domain scores are the mean scores of each domain.

The global score is the mean of all 12 items.

Appendix 8 - Quality of Life Score for Children with Fecal Incontinence [241]

Item	Criteria	Points
Soiling	Absent	4
	Accidental	3
	Frequent	2
Incontinence	Accidental	1
	Frequent	0
School absence	Never	2
	Accidental	1
	Frequent	0
Unhappy or anxious	Never	2
	Accidental	1
	Frequent	0
Food restriction	No	2
	Somewhat	1
	Much	0
Peer rejection	Never	2
	Accidental	1
	Frequent	0

NOTE. The higher the scores, the better the quality of life. (Max. score 13)

Appendix 9 - Pediatric Quality of Life Questionnaire (PedsQL)[255]

Child report (ages 8-12) (below)
Teen report (ages 13-18)

Parent report for children (ages 8-12)
Parent report for teens (ages 13-18)

Directions

On the following page is a list of things that might be a problem for you.
Please tell us **how much of a problem** each one has been for you during the **pas ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

ABOUT MY HEALTH AND ACTIVITIES (problems with.....)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS (problems with.....)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS (problems with…..)	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard for me to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL (problems with…..)	Never	Almost Never	Someti mes	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

Appendix 10 - Recruitment flyer for TIC TOC Trial participants

TIC TOC

"...resetting the colonic clock..."

We are looking for volunteers (aged 8-18) to take part in a study at the Royal Children's Hospital to look at the effectiveness of a new treatment for constipation

Children must have been diagnosed with Slow Transit Constipation (STC) and have undergone a minimum of 2 years of treatment

The study involves stimulating the nerves to the bowel to see if this improves the way it empties.

The therapy will take the form of painless electrical stimulation delivered through the skin by electrodes placed on the tummy and back

This study follows up on a pilot study performed in 2002 from which the results are encouraging

Anyone interested in finding out more about the study should contact Janet Chase or Melanie Clarke on 9345 6458 (office hours) or 9345 5805 (out of hours) or e-mail - mccclarke@hotmail.com

Thank you

Appendix 11 - Randomisation letter for Physiotherapist

THE UNIVERSITY OF MELBOURNE

Murdoch Childrens Research Institute

ROYAL CHILDREN'S HOSPITAL

TIC TOC

Dear Participating Physiotherapist,

Thank you for agreeing to take part in the TIC TOC trial. The child whose name appears on the outside of this envelope has randomly been allocated to receive IFT from **Machine A**.

Please do not discuss this information with anyone involved in the trial (including coordinators and patients/family members) as all involved (apart from yourselves) have been blinded to the treatment selection.

Thank you again.

Patient code name/no_____ **Therapist**_____ **Location** _____

Prior to starting IFT: confirm patient is suitable
Check skin intact and no local sensory loss.

Parameters Sub motor intensity
80-150 beat frequency,4kHz carrier frequency
4 pole
Surge off, Vector rotation off

New electrodes each occasion
Size 50X50 mm

Session	Date	Machine	Parameters as above	Pre-skin check	Skin prep	Electrode location checked	Warning given	Max intensity (mA)	Tingling felt	Post-skin check	Comments re session or patient response
1		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
2		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
3		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
4		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
5		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
6		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
7		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
8		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
9		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
10		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
11		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		
12		A or B	Yes No		Alcohol or Wash	Yes No	Yes No		Yes No		

Dosage - 12 sessions altogether. 3 per week for 4 weeks. **Circle what you did after each session**

WHEN THIS CHECKLIST IS COMPLETE PLEASE POST IT IMMEDIATELY IN THE STAMPED SELF-ADDRESSED ENVELOPE PROVIDED

Appendix 13 - Physiotherapist instruction pack

THE UNIVERSITY OF MELBOURNE

Murdoch Childrens Research Institute

ROYAL CHILDREN'S HOSPITAL

TIC TOC TRIAL

Dear _____

Thank you for agreeing to be part of the TIC TOC trial which is a NHMRC funded trial aimed at investigating the effect of 2 levels of current (IFT A & B) on bowel motility in children with slow transit constipation. The trial design is as follows:

An initial assessment is done by Dr Susie Gibb, Janet Chase and Melanie Clarke followed by 4 weeks of baseline recording of bowel function.

Treatment then occurs in 5 steps:
Step 1 - 4 weeks of bowel stimulation using one level of current
Step 2 - 2 months of bowel diary
Step 3 - 4 weeks of bowel stimulation with the other level of current
Step 4 - 2 months of bowel diary
Step 5 – Contact at 3, 6 and 12 months after therapy to see how they are progressing

Your role is to administer the IFT according to the directions on the following pages.

As we are aiming to eliminate any confounding factors in this trial such as therapist/patient relationship, we are asking you to act as a technician rather than a therapist, and not to give any advice, other treatment, expectations or feedback as to whether you think IFT will be, or is being effective.

Our main outcome measure is the child's bowel diary and your encouraging the child/family to continue to fill this in would be very helpful and very much appreciated.

If you have concerns about either the child or equipment please contact us on the following numbers.

Janet Chase:	Ph: 92651401 Monday and Tuesday Ph: 9345 6458 Wednesday and Thursday or 9345 5805 (and leave a message)
Melanie Clarke:	Ph: 9345 6458 or 9345 5522 pager 6655
Susie Gibb:	Ph: Paging service 93871000

Equipment
2 Metron interferential (IFT) machines, labelled A or B on the base of the machines, will be supplied by the researchers.

You will be contacted by phone to set up appointments for the child, and by letter with the randomisation results as to whether IFT A or B is to be used.

This must not be discussed with the child/family or the researchers who are to remain blinded to this information.

Every application must be done the same way as far as possible. One machine has a standard output (machine A) and the delivers no current (machine B). This means that during the output check nothing will be felt with one machine whereas the other will be standard. Note: the output meter on both will still register.

Protocol
(Standard protocol for electrical stimulation as per the APA, EPA Guidelines 2001[1])

Confirm patient is suitable.
Check skin intact & normally innervated in electrode placement area, no indwelling stimulator, and patient understands what is being done and is willing to have stimulation.

Vectorsurge 5	Settings
Output selection	
Program recall/store	Store to recall each time
Output display	Either
Patient mode	Single
Output mode -IFT, Tens or Russian	IFT
Treatment time	20 min
Surge	Off
Sweep range	80-150
Output configuration -4 pole or 2 pole	4 pole
Frequency 2.5, 4 or 10	4kHz
Vector rotation	Off

Output check
Turn on stimulator. Test the stimulator output on operator's hand/forearm. (Note: Both machines will have an output show on the meter but you will not feel it on machine B. If you have any concerns, contact Janet Chase).

After testing, leave stimulator on with the output at zero.

[1] Robertson, V. J., Chipchase, L., Laakso, E., Whelan, K., & McKenna, L. (2001). *Guidelines for the clinical use of electrophysical agents.* Melbourne: Australian Physiotherapy Association.

Skin preparation
Alcohol wipes where electrodes are to go, OR soap and water, rinse & pat dry – for more details see below.

Electrodes
New, self adhesive sized: 50 x 50 mm (if you consider the size is not large enough for older children, contact Janet Chase).

Locations: Anterior electrodes - 1 midway along and just below each costal margin.
Posterior electrodes - over erector spinae muscle midway between T9 and L2.

Connect each posterior electrode to a lead to contralateral anterior electrode.

Before beginning treatment
As per usual, warn the patient:

When I turn it up you might feel a tingling or no particular feeling. If you feel anything or you can feel muscles twitching, let me know immediately as it's important it stays low and must be comfortable. Do you understand what I have said? Do you have any questions? Are you happy for me to proceed? (Based on EPA Guidelines 2001, p7)

Intensity
Gradually turn up intensity until patient says can feel tingling or, if no such feeling, to no more than halfway on the output dial (ie, 30mA).

If feels tingling: check after 2 to 5 minutes and turn up if necessary to maintain that response. Record the final intensity setting (mA).

If feels no tingling: check after 2 to 5 minutes and turn output up to 40mA. Record this level as max intensity (mA).

Leave on for 20 minutes. Check skin after removing electrodes.

Record
Complete tick box sheet (attached).

Appointments
12 sessions: 3 per week for 4 weeks.

AT THE END OF 12 SESSIONS PLEASE POST THE CHECKLIST IN THE STAMPED SELF- ADDRESSED ENVELOPE PROVIDED FOR YOU

DETAILS OF ELECTRODE PLACEMENT AND CARE

Clean the skin where the electrodes go
Use soap & water & pat dry, or, just an alcohol wipe.

Self Adhesive Electrodes
Open the packet and connect one pigtail to a lead.
Gently peel that electrode off its backing and put on the right place on the skin. [Don't use the pigtail for this as it may pull the wire out of the electrode.]
Smooth the electrode on the skin so it sticks all over and is flat on the skin.

Repeat so you have all 4 electrodes on the skin - 2 paraspinally T10-11 to L2 and 2 on the anterior abdominal wall (attach to contralateral electrodes - usual IFT arrangement) either side of the umbilicus just below the costal margin. If the child has a stoma the electrode position may need to be adjusted slightly so it does not lie directly over the stoma. Leads are attached so that each posterior electrode crosses diagonally with its anterior "mate".

When it's time to take the electrodes off
Carefully peel off one electrode. Stick back onto its backing plastic. Hold the pigtale and pull the connection out. Repeat with the other 3 electrodes in turn. Check the underlying skin. It might be slightly red - that is usual. Anything else, contact Janet Chase.

Care of self adhesive electrodes
Keep on the plastic backing in its sealable **named** plastic bag between uses.
After each use - put electrode back onto the backing it came on
- exclude all air bubbles between the electrode and backing
- add 4 or 5 drips of water to the backing - NO more.

Place electrodes in named plastic bag - exclude air and seal. Store flat.

Cared for this way, self adhesive electrodes will last for many uses.

When to throw out an electrode
DO NOT use an electrode if it does not stick all over to the skin.
When a corner starts to peel off it when you put it on the skin, throw it away and use a new electrode.
Electrodes should only be reused on the same person.

Regarding payment
Your account for each child treated should be sent to:
Dr Bridget Southwell
Murdoch Childrens Research Institute
Flemington Rd
Parkville 3052

We suggest that the easiest way of doing this is at the end of 12 sessions, not after each treatment.

Please feel free to contact me at any stage. Thank you very much for participating.

WE ARE VERY GRATEFUL FOR YOUR ASSISTANCE WITH THIS PROTOCOL

If you have any comments, please let us know. Remember, we need trial coordinators and the child/family NOT to know which IFT machine is being used.

TIC TOC - FAQs regarding use of IFT

1. There is a problem as no output reading showing (mA)
ANSWER: If no output reading when standard testing on therapist performed there is a problem. Machine should be checked. Contact Janet Chase.

2. Missed a set appointment. Do we make it up over time or leave it.
ANSWER: If one appointment missed, add an extra as soon as possible so 12 within 4 weeks. No more than 4 IFT treatments in any 1week.

3. Patient thinks there is a problem as cannot feel tingling
ANSWER: This may be 1 of several things:

- cutaneous sensory problem (do sharp/blunt test - if no sensation in electrode area, patient not suitable for this study);
- the machine being used is a placebo machine (continue treatment as scheduled but please do not discuss the output level with Janet or the child/family)
- the intensity level is too low or has dropped since turned on (turn up until tingling reported again or 40mA if not tingling felt at all)
- there is a problem with the machine (contact Janet Chase).

4. Patient thinks there is a problem as can feel tingling.
ANSWER: This is expected response for an unaltered IFT machine above an intensity of 5mA.

5. Patient has had no responses after 6 treatments.
ANSWER: This may be 1 of several reasons

- response to IFT is not guaranteed and may not happen
- study is comparing 2 types of stimulation and 1 may be more effective in some children
- response may take longer than 6 sessions.

Continue until 12 sessions and encourage the child to continue with their diary.

6. What parameters should I be using?

- beat frequency 80-150Hz
- carrier frequency 4kHz
- 4 pole ('true' IFT)
- no surge
- no vector rotation (ie, scanning)

Appendix 14 - Parent information statement

PARENT/GUARDIAN INFORMATION STATEMENT AND CONSENT FORM

Project Number: 23040B

Title of Project: Colonic manometry and transcutaneous stimulation (using interferential therapy) in Slow Transit Constipation.

Investigators: B Southwell, J Hutson, S Gibb, A Catto-Smith, J Chase, V Robertson, M Clarke

Thank you for taking the time to read this Information Statement.

This information statement and consent is **7** pages long. Please make sure you have all the pages.

For people who speak languages other than English:
If you would also like information about the research and the Consent Form in your language, please ask the person explaining this project to you.

Your child is invited to participate in a Research Project that is explained below.

What is an Information Statement?

These pages contain information about a research project we are inviting your child to take part in. The purpose of this information is to explain to you clearly and openly all the steps and procedures of this project. The information is to help you to decide whether or not you would like your child to take part in the research.

Please read this information carefully. You can ask us questions about anything in it. You may also wish to talk about the project with others eg friends or health care worker. Once you have understood what the project is about, if you would like your child to take part please sign the consent form at the end of this information statement. You will be given a copy of this information and consent form to keep

What is the Research Project about?
Slow Transit Constipation (STC) has been recognised as an important cause of constipation in children. Treatment is improving but many children still suffer problems on a daily basis.

Children with STC have differences in the nerve systems in their bowel wall and therefore have abnormal bowel movements. We want to see if stimulating the nerves to the bowel will improve the way the bowel works. The therapy will be painless electrical stimulation that will be delivered through the skin by electrodes placed on the tummy and back.

This treatment has already been widely used for a variety of conditions and is very safe. The machine we are going to use is currently approved by the Australian Government for use in physiotherapy.

In a similar study at the Royal Children's Hospital in 2002, 6 of 8 children with STC who had this treatment had a significant improvement in their bowel symptoms. None of these children had any side effects from the treatment.

We now need to find out just how effective the treatment is and what level of stimulation is needed to produce results.

We are hoping that 80 children will take part in the study over a 3 year period. We want to compare the effectiveness of two levels of treatment. They will receive both levels of treatment in a random order. We will assess their response by a combination of daily bowel habit recording, answering questionnaires and bowel transit studies.

The exact schedule is explained later under "What does my child need to do to be in this research project".

Patients with an existing appendicostomy – If your child has an appendix stoma they will be asked if they are willing to take part in a more involved study of their bowel movements. This will involve looking at their bowels' ability to squeeze. This can be measured by what is called *manometry*. This is explained in more detail under "What does my child need to do to be in this research project".

The project is not sponsored by the company responsible for the production of the stimulator machines. The project was started by Ms Janet Chase, Dr Susie Gibb and Profesor John Hutson. None of them have a financial interest in the project.

Who are the Researchers?
Dr Susie Gibb, who is a Paediatrician from Continence Clinic, will assess children for entry into the trial.
Ms Janet Chase, who is a continence physiotherapist, will assess children before and during the trial.
Dr Melanie Clarke, who is a trainee surgeon doing an MD, will perform measurements of bowel activity.
Regional physiotherapists will perform the stimulations.

This Trial is funded by the National Health and Medical Research Council. Four senior researchers have designed this trial and raised the funds for the trial. They are Dr Bridget Southwell, Prof John Hutson, A/Prof Tony Catto-Smith and Prof Val Robertson. Dr Bridget Southwell, who is a Scientific Research Fellow and expert in the nervous system of the gut, will coordinate the trial. Prof. John Hutson, who is an expert in intestinal surgery, treats

many of the patients with STC. A/Prof. Tony Catto-Smith, who is a Gastroenterologist with experience in measuring bowel activity, will oversee the manometry measurements. Prof. Val Robertson, who is a physiotherapist expert in measuring the effects of electrical stimulation and is located in Newcastle NSW, will give independent analysis of the data.

Why is my child being asked to be in this research project?
Your child has been shown to have Slow Transit Constipation (STC). We want to see if this treatment improves the function of their bowel.

If your child has an existing appendicostomy we would like to measure the ability of their bowel to squeeze and see if this ability is affected by the treatment.

We would like to talk to you and your child and explain the study in a way that is easy for you both to understand.

What are my child's alternatives to participating in this project?
The decision to take part in this project is entirely your and your child's own choice. There are no penalties for deciding not to take part, and their future treatment will not be affected.

If your child has an existing appendicostomy, they can have the stimulation therapy even if they do not wish to participate in the manometry studies. They will receive the same treatment as the other children in the study.

What does my child need to do to be in this research project?
Once you have agreed to take part in the research project you and your child will have an initial assessment with a paediatrician and a physiotherapist. You will both be asked some questions and your child will have a check-up. Part of this assessment will involve your child having a heart tracing (ECG) and blood pressure measurements. We will also be performing an abdominal ultrasound scan. Your child will need to have a *bowel transit study* (if they have not already had one). At this stage you and your child will be asked to start a *diary* that contains details of their bowel habits and you will need to keep filling this in every day throughout the study. This is very important.

Your child will then be put into one of two groups by chance (similar to tossing a coin) to determine in which order they receive their therapy. Neither you nor your child will be able to tell which level they are getting.

4 weeks after starting the diary, your child will receive their first course of *treatment*. This will be 12 half hour sessions (3 times a weeks for 4 weeks).

After the first treatment phase we will *reassess* your child over a 2 month period. This will involve a repeat check-up and some more questions. They will also have another bowel transit study. You will both need to keep filling in their diary.

They will then receive a second session of *treatment*, but this time at the other level of stimulation. This will also be 12 half hour sessions (3 times a week for 4 weeks).

After the second treatment phase there will be another 2 month period of *reassessment*. During this period you must continue to complete their toilet diary. They will have another check-up and both of you will again be asked some questions. Your child may be asked to have another bowel transit study.

We will contact you and your child at 3, 6 and 12 months after finishing the treatment. This will be your *follow-up* and we will simply ask you both some more questions.

If your child has an existing appendicostomy and has agreed to take part in the *manometry* (pressure recording) studies, this will involve a bit of extra time. Before starting the treatment (as part of the *initial assessment*) they will have their first study. For each study they will need to come into the surgical ward at the Royal Children's Hospital for 2 nights. In order to measure the squeezing that happens in their bowel, we will put a thin plastic tube in through their appendicostomy and allow it to travel along the bowel together with any washout/poo. When the tube is in the right place we will connect the other end to a recording machine for 24 hours and measure how many times their bowel squeezes and how strong the squeezes are. During this time they will be able to eat and drink normally but they will not be able to move around a lot as they are attached to the machine.

We will ask them to have another manometry study after they have had the first course of therapy so see how it has affected the squeezing ability of their bowel.

The project will undergo continual review and monitoring. We are committed to the safety and efficiency of this project and will attempt to detect any problems affecting you or your child. We very much appreciate the considerable time required of you both for your participation.

Is there likely to be a benefit to my child?
The results of our previous study suggest that this treatment may be effective in managing bowel symptoms of children with STC. It is possible that the treatment will increase the ability of their bowel to empty. This could potentially reduce your child's soiling and their need for medication and, in those with appendicostomies, their need for washouts.

Is there likely to be a benefit to other people in the future?
We hope that electrical therapy will be useful in the treatment of many children with STC. Current treatment involves frequent visits to hospital and may even involve the need for surgery. This treatment could improve children's lives.

Even if the treatment proves to be less effective than we expect, the information that we gain will greatly advance what we know about constipation in children.

What are the possible risks and/or side-effects?
Electrical therapy has no known side effects. To date none of the children who have received electrical stimulation have experienced any side effects; however there could be as yet unknown side effects. We will monitor closely for any possibility of these occurring.

All of the children who have had manometry studies have tolerated the procedure very well. We do not anticipate any risks or side effects.

What are the possible discomforts and/or inconveniences?
The electrical therapy may cause a tingling sensation in the skin under the electrodes. This stops as soon as the machine is switched off. Your child may find the sensation unusual but it should not be uncomfortable.

With the manometry study, some children have had some abdominal cramps when the tube passes around the bowel due to the stimulant that is used to help advance the tube. If at any stage your child becomes too uncomfortable we will stop the test.

Taking part does involve a considerable amount of dedication and time. It is essential that you and your child provide us with as much information as possible so that we can get the most out of the study.

What will be done to make sure the information is confidential?
All study information will be numbered and kept separately from any names and addresses. Any results that are published will not include your child's name.

Will I be informed of the results when the research project is finished?
The results of your child's therapy and/or tests will be discussed with you both at the end of the project. You will also be told about the results of the whole study. We also intend to publish the results in the NIDKIDs and GGLF newsletters and on the NIDKIDs website.

You can decide whether or not to give permission for your child to take part in this research project. You can decide whether or not you would like to withdraw your child at any time without explanation.

You may like to discuss your child's participation in this research project with your family and with your doctor. You can ask for further information before deciding to take part.

If you would like more information about the study or if you need to contact a study representative in an emergency, the person to contact is:

Name: Professor John Hutson

Contact telephone: 03 9345 5805 (W)

What are my child's rights as a participant?

1. I am informed that except where stated above, no information regarding my child's medical history will be released. This is subject to legal requirements.

2. I am informed that the results of any tests involving my child will not be published so as to reveal my child's identity. This is subject to legal requirements.

3. The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.

4. It has also been explained that my child's involvement in the research may not be of any benefit to him or her. I understand that the purpose of this research project is to improve the quality of medical care in the future.

5. I have been asked if I would like to have a family member or a friend with me while the project is explained to me.

6. I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).

7. I understand that this research project has been approved by The Royal Children's Hospital Ethics in Human Research Committee on behalf of The Royal Children's Hospital Board.

8. I have received a copy of this document.

If you have any concerns about the study, and would like to speak to someone independent of the study, please contact The RCH Consumer Liaison, Clinical Support Services Team at the Executive Office. Telephone 9345 5676 (Monday to Friday 9am-5pm).

STANDARD INFORMED CONSENT FOR PARENT/GUARDIAN TO GIVE CONSENT FOR THEIR CHILD TO PARTICIPATE IN A RESEARCH PROJECT

Project Number

Title of Project

Investigator(s)

I (Parent/Guardian name)

voluntarily consent for my child _____to take part in the above titled
Research Project, explained to me by

Mr/Ms/Dr/Professor

- I have received a Parent/Guardian Information Statement to keep and I believe I understand the purpose, extent and possible effects of my child's involvement
- I have been asked if I would like to have a family member or friend with me while the project was explained
- I have had an opportunity to ask questions and I am satisfied with the answers I have received
- I understand that the researcher has agreed not to reveal results of any information involving my child, subject to legal requirements
- If information about this project is published or presented in any public form, I understand that the researcher will not reveal my child's identity
- I understand that if I refuse to consent to my child's participation, or if I withdraw my child from the project at any time without explanation, this will not affect my child's access to the best available treatment options and care from The Royal Children's Hospital
- I understand I will receive a copy of this consent form

SIGNATURE _____ Date _____

I have explained the study to the parent/guardian who has signed above, and believe that they understand the purpose, extent and possible effects of their child's involvement in this study.

RESEARCHER'S SIGNATURE _____ Date _____

Note: All parties signing the Consent Form must date their own signature.

Appendix 15 - Participant information statement

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

Project Number: 23040B

Title of Project: Colonic manometry and transcutaneous stimulation (using interferential therapy) in Slow Transit Constipation.

Investigators: B Southwell, J Hutson, S Gibb, A Catto-Smith, J Chase, V Robertson, M Clarke

Thank you for taking the time to read this Information Statement.

This information statement and consent is **8** pages long. Please make sure you have all the pages.

For people who speak languages other than English:
If you would also like information about the research and the Consent Form in your language, please ask the person explaining this project to you.

You are invited to participate in a Research Project that is explained below.

What is an Information Statement?

These pages contain information about a research project we are inviting you to take part in. The purpose of this information is to explain to you clearly and openly all the steps and procedures of this project. The information is to help you to decide whether or not you would like to take part in the research.

Please read this information carefully. You can ask us questions about anything in it. You may also wish to talk about the project with your parents or guardians, friends or health care worker. Once you have understood what the project is about, if you wish to take part please sign the consent form at the end of this information statement. You will be given a copy of this information and consent form to keep.

What is the Research Project about?
Slow Transit Constipation (STC) has been recognised as an important cause of constipation in children. Treatment is improving but many of you still suffer problems on a daily basis.

Children with STC have differences in the nerve systems in their bowel wall and therefore have abnormal bowel movements. We want to see if stimulating the nerves to the bowel will improve the way the bowel works. The therapy will be painless electrical stimulation that will be delivered through the skin by electrodes placed on the tummy and back.

This treatment has already been widely used for a variety of conditions and is very safe. The machine we are going to use is currently approved by the Australian Government for use in physiotherapy.

In a similar study at the Royal Children's Hospital in 2002, 6 of 8 children with STC who had this treatment had a significant improvement in their bowel symptoms. None of these children had any side effects from the treatment.

We now need to find out just how effective the treatment is and what level of stimulation is needed to produce results.

We are hoping that 80 children will take part in the study over a 3 year period. We want to compare the effectiveness of two levels of treatment. You will receive both levels of treatment in a random order. We will assess your response by a combination of daily bowel habit recording, answering questionnaires and bowel transit studies.

The exact schedule is explained later under "What do I need to do to be in this research project".

Patients with an existing appendicostomy – If you have an appendix stoma you will be asked if you are willing to take part in a more involved study of your bowel movements. This will involve looking at your bowels ability to squeeze. This can be measured by what is called *manometry*. This is explained in more detail under "What do I need to do to be in this research project".

The project is not sponsored by the company responsible for the production of the stimulator machines. The project was started by Ms Janet Chase, Dr Susie Gibb and Profesor John Hutson. None of them have a financial interest in the project.

Who are the Researchers?
Dr Susie Gibb, who is a Paediatrician from the Continence Clinic, will assess children for entry into the trial.
Ms Janet Chase, who is a continence physiotherapist, will assess children before and during the trial.
Dr Melanie Clarke, who is a trainee surgeon doing an MD, will perform measurements of bowel activity.
Regional physiotherapists will perform the stimulations.

This Trial is funded by the National Health and Medical Research Council. Four senior researchers have designed this trial and raised the funds for the trial. They are Dr Bridget Southwell, Prof John Hutson, A/Prof Tony Catto-Smith and Prof Val Robertson. Dr Bridget Southwell, who is a Scientific Research Fellow and expert in the nervous system of the gut, will coordinate the trial. Prof. John Hutson, who is an expert in intestinal surgery, treats many of the patients with STC. A/Prof. Tony Catto-Smith, who is a Gastroenterologist with

experience in measuring bowel activity, will oversee manometry measurments. Prof. Val Robertson, who is a physiotherapist expert in measuring the effects of electrical stimulation and is located in Newcastle NSW, will give independent analysis of the data.

Why am I being asked to be in this research project?

You have been shown to have Slow Transit Constipation (STC). We want to see if this treatment improves the function of your bowel.

If you have an existing appendicostomy we would like to measure the ability of your bowel to squeeze and see if this ability is affected by the treatment.

We would like to talk to you and explain the study in a way that is easy for you to understand.

What are the alternatives to participating in this project?

The decision to take part in this project is entirely your own choice. There are no penalties for deciding not to take part, and your future treatment will not be affected.

If you have an existing appendicostomy, you can have the stimulation therapy even if you do not wish to participate in the manometry studies. You will receive the same treatment as the other children in the study.

What do I need to do to be in this research project?

Once you have agreed to take part in the research project you will have an *initial assessment* with a doctor and a physiotherapist. You will be asked some questions and will have a check-up. As part of this assessment we will measure your blood pressure and do a heart tracing (ECG). We will also be doing an ultrasound scan of your tummy. You will need to have a *bowel transit study* (if you have not already had one). You will be asked to start a *diary* that contains details of your pooing habits and you will need to keep filling this in every day throughout the study. This is very important.

4 weeks after starting your diary, you will receive your first course of *treatment*. This will be 12 half hour sessions (3 times a weeks for 4 weeks).

After the first treatment phase we will *reassess* you over a 2 month period. This will involve a repeat check-up and some more questions. You will also have another bowel transit study. You will need to keep filling in your diary.

You will then receive a second session of *treatment*, but this time at the other level of stimulation. This will also be 12 half hour sessions (3 times a week for 4 weeks).

After the second treatment phase there will be another 2 month period of *reassessment*. You must still fill in your diary. You will have another check-up and will again be asked some questions. You may be asked to have another bowel transit study.

What do I need to do to be in this research project?

Initial Assessment

Bowel Transit Study

Examination

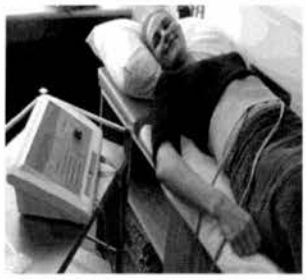
Questionnaire

Toilet Diary - You will start this 4 weeks before having any therapy and will keep it going for the whole treatment period

Treatment - This will be a 5-step programme

Step 1 **First Course of Bowel Stimulation -** 12 half-hour sessions (3 times a week) over 4 weeks. We will connect you to a machine by wires applied painlessly to the skin of the tummy and back

Step 2 **Re-Assessment Over 2 Months**



Step 3 **Second Course of Bowel Stimulation -** 12 half-hour sessions (3 times a week) over 4 weeks

Step 4 **Re-Assessment Over 2 Months**

Step 5 **Follow Up -** Contact at 3, 6 and 12 months after therapy (questionnaires and examinations)

We will contact you at 3, 6 and 12 months after finishing the treatment. This will be your *follow-up* and we will simply ask you some more questions.

If you have an existing appendicostomy and have agreed to take part in the *manometry* studies, this will involve a bit of extra time. Before starting the treatment (as part of the *initial assessment*) you will have your first study. For each study you will need to come into the surgical ward at the Royal Children's Hospital for 2 nights. In order to measure the squeezing that happens in your bowel, we will put a thin plastic tube in through your appendicostomy and allow it to travel along the bowel together with any washout/poo. When the tube is in the right place we will connect the other end to a recording machine for 24 hours and measure how many times your bowel squeezes and how strong the squeezes are. During this time you will be able to eat and drink normally but you will not be able to move around a lot as you are attached to the machine.

We will ask you to have another manometry study after you have had the first course of therapy to see how it has affected the squeezing ability of your bowel.

The project will undergo continual review and monitoring. We are committed to the safety and efficiency of this project and will attempt to detect any problems affecting you. We very much appreciate the considerable time required of you for your participation.

Is there likely to be a benefit to me?

The results of our previous study suggest that this treatment may be effective in managing your bowel symptoms. It is possible that the treatment will increase your bowel emptying. This may reduce your soiling and need for medication and, in those of you with appendicostomies, your need for washouts.

Is there likely to be a benefit to other people in the future?

We hope that electrical therapy will be useful in the treatment of many children with STC. Current treatment involves frequent visits to hospital and may even involve the need for surgery. This treatment could improve children's lives.

Even if the treatment proves to be less effective than we expect, the information that you give us will greatly advance what we know about constipation in children.

What are the possible risks and/or side-effects?

Electrical therapy has no known side effects. To date none of the children who have received electrical stimulation have experienced any side effects; however there could be as yet unknown side effects. We will monitor closely for any possibility of these occurring.

All of the children who have had manometry studies have tolerated the procedure very well. We do not anticipate any risks or side effects.

What are the possible discomforts and/or inconveniences?

The electrical therapy may cause a tingling sensation in the skin under the electrodes. This stops as soon as the machine is switched off. You may find the sensation unusual but it should not be uncomfortable.

With the manometry study, some children have had some tummy cramps when the tube passes around the bowel due to the stimulant that is used to help the tube to move. If at any stage you become too uncomfortable we will stop the test.

Taking part does involve a considerable amount of dedication and time. It is essential that you provide us with as much information as possible so that we can get the most out of the study.

What will be done to make sure the information is confidential?

Your study information will be numbered and kept separately from any of your names and addresses. Any results that are published will not include your names.

Will I be informed of the results when the research project is finished?

The results of your therapy and/or tests will be discussed with you at the end of the project. You will also be told about the results of the whole study. We also intend to publish the results in the NIDKIDs and GGLF newsletters and on the NIDKIDs website.

You can decide whether or not to take part in this research project. You can decide whether or not you would like to withdraw at any time without explanation.

You may like to discuss participation in this research project with your family and with your doctor. You can ask for further information before deciding to take part.

If you would like more information about the study or if you need to contact a study representative in an emergency, the person to contact is:

Name: Prof. John Hutson

Contact telephone: 03 9345 5805 (W)

What are my rights as a participant?

1. I am informed that except where stated above, no information regarding my medical history will be released. This is subject to legal requirements.

2. I am informed that the results of any tests involving me will not be published so as to reveal my identity. This is subject to legal requirements.

3. The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.

4. It has also been explained that my involvement in the research may not be of any benefit to me personally. I understand that the purpose of this research project is to improve the quality of medical care in the future.

5. I have been asked if I would like to have a family member or a friend with me while the project is explained to me.

6. I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).

7. I understand that this research project has been approved by The Royal Children's Hospital Ethics in Human Research Committee on behalf of The Royal Children's Hospital Board.

8. I have received a copy of this document.

If you have any concerns about the study, and would like to speak to someone independent of the study, please contact The RCH Consumer Liaison, Clinical Support Services Team at the Executive Office. Telephone 9345 5676 (Monday to Friday 9am-5pm).

STANDARD INFORMED CONSENT FOR PARTICIPANT TO PARTICIPATE IN A RESEARCH PROJECT

Project Number

Title of Project

Principal Investigator(s)

I (Parent/Guardian name)

voluntarily consent for my child _____ to take part in the above titled
Research Project, explained to me by

Mr/Ms/Dr/Professor

- I have received a Participant Information Statement to keep and I believe I understand the purpose, extent and possible effects of my involvement
- I have been asked if I would like to have a family member or friend with me while the project was explained
- I have had an opportunity to ask questions and I am satisfied with the answers I have received
- I understand that the researcher has agreed not to reveal results of any information involving me, subject to legal requirements
- If information about this project is published or presented in any public form, I understand that the researcher will not reveal my identity
- I understand that if I refuse to consent, or if I withdraw from the study at any time without explanation, this will not affect my access to the best available treatment options and care from The Royal Children's Hospital
- I understand I will receive a copy of this consent form

SIGNATURE _____ Date _____

I have explained the study to the participant who has signed above, and believe that they understand the purpose, extent and possible effects of their involvement in this study.

RESEARCHER'S SIGNATURE _____ Date _____

Note: All parties signing the Consent Form must date their own signature.

Appendix 16 - Medical Assessment Data Sheet

TIC TOC Trial Medical Assessment Data Sheet

Demographics

UR:
Study number:
Name:
DOB:
Home phone:
Parents names:

Email:
Mobile:
Parent's mobile:
Parent's email:

Medical History

Diagnosis

Age of onset symptoms:
Date of diagnosis of STC:

Transit study:	Yes/No	Result	Date
Biopsies:	Yes/No	Result	Date

History

Neonatal (inc passage of meconium):

.....
.....
.....

Developmental:

.....
.....
.....

Other conditions excluded:	Hirschsprungs	Yes/No
	Hypothyroidism	Yes/No
	Coeliac disease	Yes/No
	Allergy	Yes/No

Symptoms

Current bladder symptoms: Day: urgency (Y/N), wetting (Y/N), posturing Y/N), frequency (Y/N), hesitancy (Y/N), straining to void (Y/N), infrequent voiding (Y/N)

Night: wetting (Y/N), nocturia (Y/N)

If bladder symptoms are present - how often are they occurring?

.....
.....
.....

Current bowel symptoms:	Stools:	Frequency	Type
	Soiling:	Frequency	Amount
	Pain:	Yes/No	Frequency
	Rectal awareness:	Full/Partial/None	

Treatments

Toileting programme	Yes/No	Date	Result
Previous physio	Yes/No	Date	Result
Previous treatments:	Softeners (Y/N), Osmotic agents (Y/N), Movicol (Y/N), Stimulants (Y/N), NG washouts (Y/N), Enemas (Y/N), Appendicostomy (Y/N), Other.....		

Current treatment regime:

.....
.....

Physical examination

Height:..... Weight:.....

BP lying:..... BP standing:.....

Pulse lying:..... Pulse standing:.....

General inspection:

.....
.....
.....

Abdominal examination:

Distension	Yes/No
Hepatosplenomegaly	Yes/No
Abdominal mass - inc faecaloma	Yes/No
Palpable bowel loops	Yes/No

Neurological and spinal examination:

Lower limb:	Tone	Normal/Abnormal
	Reflexes	Normal/Abnormal
	Power	Normal/Abnormal
Sacral dimple/sacral hair tuft		Yes/No
Obvious spinal deformity		Yes/No
Muscle (esp buttock) wasting		Yes/No

Anal inspection:

Site	Normal/Abnormal
Visible stool (skin and clothing)	Yes/No
Skin condition	.....
Perianal skin tags	Yes/No
Anal fissure	Yes/No

Check list

No previous electrical therapy: Yes/No

Decision: Enrol Yes/No

Exclusions Yes/No
(please state).....
.....

Investigations needed Yes/No
(please list).....
.....

Appendix 17 - Visual Analogue Scale for Assessment of Rectal Perception

Date:

Code name:

Question:

In the last week have you had any feeling in your bottom of needing to do a poo?

0 |_____| 10

none — strong and definite feeling to poo

Appendix 18 - Bowel diary

WELCOME TO THE TIC TOC TRIAL

.....and thank you for being part of it. We hope that you enjoy your involvement and we look forward to getting to know you better.

If at any time you have any questions or problems in regard to the trial, do not hesitate to phone us.

Janet Chase:	Ph: 9345 6458 Wednesday and Thursday or 9345 5805
Susie Gibb:	Ph: Paging service 93871000

On the next page you will find an explanation of how to fill in you bowel diary. You need to do this every day throughout the trial, so this will take a lot of commitment and hard work on your part, even though it should only take 1-2 minutes per day to do.

Below is a summary of how the trial works. This is also explained in The Participant Information Statement that you have already been given.

Initial assessment involves a bowel transit study (if you haven't already had one), and a check-up by Susie Gibb and a look at your back and tummy muscles and posture by Janet Chase.

Treatment occurs in 5 steps
Step 1 - 4 weeks of bowel stimulation using one form of current
Step 2 - 2 months of bowel diary
Step 3 - 4 weeks of bowel stimulation with the other form of current
Step 4 - 2 months of bowel diary
Step 5 - We contact you 6 and 12 months after therapy to see how you are doing.

INSTRUCTIONS FOR COMPLETING THE BOWEL DIARY

In this folder you should find a copy of the Bristol Stool Scale and some of the diary pages that are colour-coded according to the stage in the trial in which you are using them - blue for pre-treatment, red for the first 4 weeks of electrical stimulation, yellow for the following 2 months, purple for the second course of electrical stimulation and green thereafter. The rest we will give you as you go along.

1 The diary ***must be*** filled in each night before you go to bed, so you can remember what happened that day.

2 Make sure that ***each*** day has a date (day/month/year) and your code name is on it. This is the name you can choose so that your real name does not appear on any paperwork.

3 Under the column headed ***"Bowel action and type"***

- put a tick (√) for each bowel action you have.
- the tick goes in the 'sit' column if it happened as the result of going to the toilet to sit without any feeling of needing to poo.
- the tick goes in the 'spontaneous' column, if you went to the toilet because you had a feeling that you needed to poo.
- 'type' refers to the number that best describes the type of poo on the Bristol Stool Scale.

4 Under the column headed ***"Soiling"***

- put an 's' for each episode of soiling during the day.
- the 's' goes in the 'stain' column if the soiling was just a stain on the underwear.
- the 's' goes in the 'scrape' column if poo had to be scraped off before the underwear could be washed.

5 The column headed ***"Tablets, medicines, suppositories, enemas, washouts"*** is where you record the medicines etc.you had that day, and whether you had a bowel washout - just write "w.o." if you did.

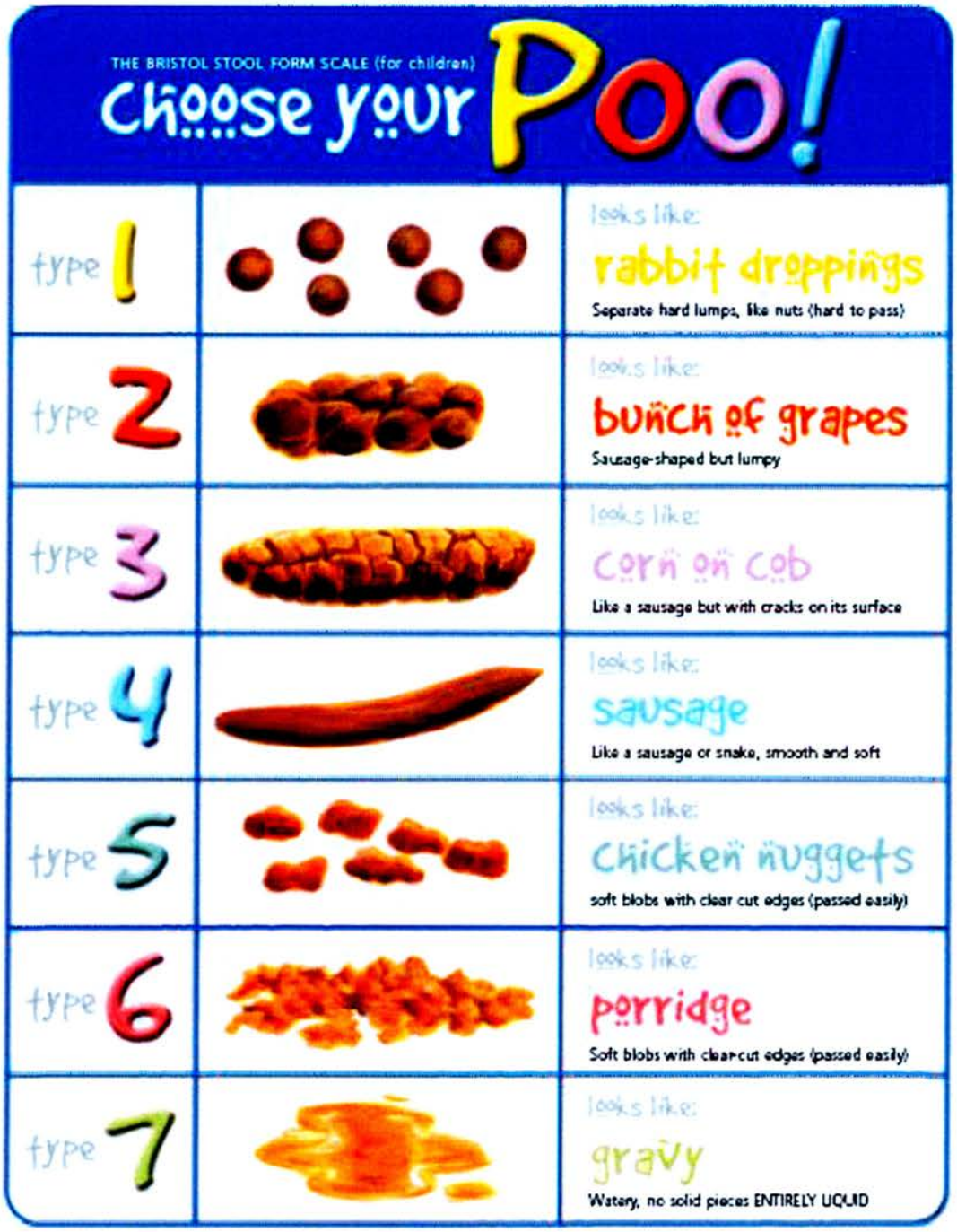
6 The column headed ***"Physio today?"*** is to record the days that you have electrical stimulation for your bowel.

7 The next column is to record whether you have ***"Tummy pain"*** or not on each particular day.

BOWEL DIARY SHEET **YOUR CODE NAME:**

Date started / /	Bowel action and type		Soiling		Medication	Physio today? Yes/no	Tummy pain today? Yes/no	Comments
	Sit	Spontan -eous	Stain	Scrape				
MONDAY								
TUESDAY								
WEDNESDAY								
THURSDAY								
FRIDAY								
SATURDAY								
SUNDAY								

Appendix 19 - Bristol Stool Scale



Appendix 20 - Bowel dysfunction questionnaire

Bowel dysfunction assessment

DEMOGRAPHICS

Date of questionnaire:-

Code name:-

Age:-

Gender:-

Diagnosis:-

Date of first symptoms:-

Date of diagnosis:-

APPENDICOSTOMY FORMATION (IF RELEVENT)

Indication:-

Formation date:-

Age (years):-

Mode of formation:-

Laparoscopy *Laparotomy*

Formation complications?

Pain *Bleeding* *Infection* *Ruptured sutures*

Other

Please comment:-

Length of stay:-

1-3 days *4-7 days* *1-2 weeks* *2-3 weeks*

Initial device used:-

Chait button *Silastic catheter* *Intermittent catheterisation*

Other

Please comment:-

Appendicostomy still in use?

Yes *No*

Cessation date:-

Reason for cessation:-

Appendicostomy removed?

Yes *No*

Date of removal:-

HOLSCHNEIDER SCORE

Frequency of defaecation?

Stool consistency?

Normal *Loose* *Liquid*

Soiling?

None *Stress/diarrhoea associated* *Constant*

Rectal sensation?

Normal *Defective* *Absent*

Ability to hold back defaecation?

Mins *Secs* *Absent*

Discrimination between formed, loose or gaseous stools?

Normal *Defective* *Absent*

Need for therapy (enemas, drugs, pads)?

None *Occasional* *Always*

TEMPLETON SCORE

Regular school attendance?

Full time *Part time* *Never*

Social limitations?

No limitations *Some self imposed or parental restrictions*

Very limited or restricted

Toilet free (can be an hour from a toilet)?

Yes *No*

Participates in any sport (no limits on swimming)?

Yes *No*

No "job" limitations?

Yes *No*

ROUTINES (NO APPENDICOSTOMY)

Does your child use laxatives?

Yes *No* *Occasionally*

What type of laxative?

Does your child require regular suppositories?

Yes *No*

Does your child require enemas?

Yes *No*

Does your child ever require disempaction?

Yes *No*

Is your child on any other treatment?

What food or drinks does you child not tolerate?

Does your child currently suffer from abdominal pain/discomfort?

Yes *No*

How frequent is the pain?

Daily *3-6 days/week* *1-2 days/week*

1-2 days/fortnight *1-2 days/month* *Every 2-3 months*

What score would you give the pain out of 10?

ROUTINES (WITH APPENDICOSTOMY)

Initial solution trialled:-

Golytely *Phosphate enemas* *Dulcolax enemas* *Plain water*

Soapy water *Salty water* *Other*

Please comment:-

Current solution used:-

CONTINENCE

How often does your child have episodes of soiling?

Never *Daily* *3-6 days/week* *1-2 days/week*

1-2 days/fortnight *1-2 days/month* *Every 2-3 months*

If using an appendicostomy, when are the soiling episodes most common?

Between washouts *Just before washouts* *Only after w*ashouts

Does your child use any protective clothing?

Pads *Nappies* *Others* *None*

How often does your child wear protective clothing?

All the time *Only during daytime* *Only during night time*

Only after washouts *Day after washouts* *Occasionally*

Does your child have any problems with urinary incontinence?

Yes *No* *Occasionally*

How often does your child have episodes of urinary incontinence?

Daily *3-6 days/week* *1-2 days/week*

1-2 days/fortnight *1-2 days/month* *Every 2-3 months*

ASPIRATIONS

When do you think that your child will stop requiring medication?

<5 years *5-10 years* *10-15 years* *15-20 years* *20-25years*

>25 years *Don't know* *When they don't need it anymore*

Appendix 21 - Instruction letter for manometry

TIC TOC Trial
Department of Surgical Research
Royal Childrens Hospital
Flemington Road
Parkville
VIC 3052

Tel: (03) 9345 6458

Dear .....,

Thank you for enrolling in the TIC TOC trial and for agreeing to take part in the bowel pressure measurement (manometry) studies.

An appointment has been made for you at the Childrens Hospital on **Wednesday 30th August**. Please can you present to admissions at 9am on Wednesday and ask that they page Melanie Clarke or Di Simpson. You will be in hospital for 3 days (Weds-Fri) with the actual study running for 24hours starting on the Thursday morning. For the duration of the study (24hrs) you will have to stay in bed and although you can have your own television and games station, remember to bring plenty of extra things to do!

You will be free to go home around lunchtime on Friday. We will explain everything to you before starting the study, and you can ask as many questions as you like at any time!

Before you attend for the study there are a few things we would like to change with your washout regime.

(i) No stimulants (ie Bisacodyl, Phosphate/Dulcolax enemas) via your appendicostomy for **5 days** before you come in.

(ii) Perform washouts on the **Sunday** and **Tuesday** prior to admission with **water only**.

If you have any questions about the manometry or anything else to do with the study, don't hesitate to contact us.

We look forward to seeing you,

Melanie Clarke
Surgical Research Fellow to Professor Hutson

Appendix 22 - Manometry menu choices

24 Hour Colonic Manometry Study Meal Options

Option 1:

Breakfast:		
White Bread	2 slices	46g
Margarine	1 tsp	5g
Peanut Butter	1 tbsp	20g
Rice Bubbles	1 cup	30g
Full Cream Milk	1 cup	250mls
Lunch:		
Meat Pie or 4 Party Pies	1 or 4	190g
Tomato Sauce	1 tbsp	25g
Iced Donut	1	80g
Chips	1 cup	95g
Dinner:		
Spaghetti Bolognese		
Spaghetti	¾ cup	90g
Meat Sauce	3 tbsp	60g
Parmesan Cheese	2 tbsp	20g
Self-Saucing Pudding	½ cup	80g
Cream	2 tbsp	40g
Chocolate Milk	2 cup	500mls

Option 2:

Breakfast:		
Full Cream Milk	1 cup	250mls
Ham	1 slice	17.5g
Cheese	1 slice	21g
Croissant	1	65g
Margarine	1.5 tbsp	15g
Lunch:		
Cheese	2 slices	42g
Tomato	¼	35g
Margarine	1 tbsp	20g
White Bread	4 slices	112g
Custard	1 cup	260g
Chocolate Milk	1 cup	250mls
Dinner:		
Grilled sausages	4	120g
Tomato sauce	1 tbsp	25g
White bread roll	1	90g
Chips	½ cup	47g

Canned pears	2 halves	180g
Chocolate milk	1 cup	250mls

Option 3:

Breakfast:

Apple	1	156G
White toast	2 slices	46g
Margarine	1 tbsp	19g
Fried eggs	2 eggs	70g
Chocolate milk	1 cup	250mls

Lunch:

Shepherd's pie	1	200g
Chips	1 cup	95g
Fruit cake	1 slice	50g
Ice cream	2 scoops	48g

Dinner:

Ham and pineapple pizza	2 slices	200g
Chocolate cake	1 slice	55g
Cream	1 tbsp	20g
Chocolate milk	2 cup	500mls

Appendix 23 - Manometry event diary

24 HOUR COLONIC MANOMETRY PATIENT DIARY

PATIENT NAME:
DATE:

Time Started	Time Finished	Activity	Comments

Examples of important activities to record:
Bowel action, bowel urgency, abdominal sensations, passing urine, eating, drinking, change of posture, change bedhead.

Appendix 24 - Plain abdominal radiograph demonstrating final position of manometry catheter and relative positions of the side holes