PRAGMATIC RANDOMISED TRIAL OF LOW VERSUS HIGH VOLUME INITIATED TRANSANAL IRRIGATION THERAPY IN ADULTS WITH CHRONIC CONSTIPATION: A FEASIBILITY STUDY

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ABSTRACT

Background

Chronic Constipation (CC) is common in adults. The effect of symptoms on quality-of-life (QOL) is significant. Trans-anal irrigation therapy has become a widely-used treatment despite a lack of robust evidence. A randomised comparison of two different methods of irrigation (the CapaCiTY 02 study) will provide valuable evidence of superiority of one system over the other. This study aims to evaluate the feasibility of conducting CapaCiTY 02. Data presented are interim findings from a single study site nested within the large multi-centre CapaCiTY 02 study.

Methods

This study was a mixed methods study involving a) a systematic review and meta-analysis of current literature data for trans-anal irrigation in chronic constipation, b) a randomised controlled trial, and c) a qualitative study of the patient experience. Participants in the trial were randomised to either high volume (HV) or low volume (LV) irrigation and underwent standardised physiological investigations. Data from the first 10 months of data collection at the Durham site were used for the feasibility study. Data were collected according to a standardised outcomes framework. The primary outcome was reduction in PAC-QOL, measured at 3 months. Qualitative interviews using a phenomenological framework were undertaken to explore the nature of the participants' lived experience of irrigation. Descriptive analysis of data enabled assessment of study feasibility.

Results

The meta-analysis of seven eligible studies reported a positive response to treatment rate of 50.4%. Trial recruitment nationally was slower than anticipated. However the recruitment rate at the Durham site met the target for individual sites. A total of 19 participants were recruited at Durham, of whom 11 reached the primary outcome visit (3 months). The overall reduction in mean PAC-QOL at three months was 0.39 (SD 0.44), with a difference between groups of 0.04. Some outcome data were incompletely recorded. Of the 19 participants, 5 (29%) discontinued treatment, after a mean time of 51 days (SD 35.2). Qualitative interviews (n=5 at 3 months, n=3 at 6 months) identified important themes regarding participants' experiences of irrigation training and home use.

Discussion

Collaboration between participating sites, combined with protocol amendments, has allowed measures to be taken to improve recruitment and recording of outcomes. This study demonstrates that the proposed methodology is feasible and acceptable to a majority of patients. The qualitative study provided a broader context to the quantitative study findings.

CONTENTS

Declaration

The study presented within this thesis is nested within a larger multi-national study. Therefore significant elements of the quantitative and qualitative methodology (Chapters 3 and 4) were developed in collaboration with numerous other parties (see list of acknowledgements). Aside from this necessary input, I can confirm that this thesis is all my own work.

Statement of copyright

Authorship and Funding

As previously stated in the declaration, this thesis was written in collaboration with a number of other parties. The study presented here is nested within a large multi-centre randomised trial (the CapaCiTY 02 trial) and both the quantitative and qualitative arms of this study utilise the methodology outlined in the CapaCiTY 02 study protocol (see appendix I). I developed the CapaCiTY 02 protocol in conjunction with my academic supervisors and the trial investigator team, and my contribution to this was significant (for example, devising the randomised comparison between high and low volume irrigation, devising the irrigation training regimen and developing the Standard Operating Procedure for irrigation, as well as developing the site feasibility questionnaire and patient-public involvement work). The protocol has been published and I am the lead author of this publication (see Appendix III). Also, the systematic review and meta-analysis was conceived and carried out by me in conjunction with my academic supervisors, and does not form part of the CapaCiTY 02

programme. Additionally, all data analysis presented here (quantitative and qualitative), as well as the critical analysis and discussion, was carried out by myself.

However, significant elements of the quantitative methodology (Chapter 3) were either written by others or adapted from existing draft editions of the protocol and grant application. These include inclusion/exclusion criteria, Study randomisation and data collection procedures, trial follow up procedures, Statistical considerations including sample size, ethics, data handling and safety reporting. The qualitative methods section of the protocol was written by my supervisor Dr Helen Close, and I used this as the basis for the methodology and theoretical framework outlined in Chapter 4. Also, data on national recruitment by site were sourced from the Pragmatic Clinical Trials Unit at Queen Mary University of London, including the graphs reproduced on page 118.

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List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
BD	Twice per day
B IPQ	Brief Illness Perception Questionnaire
BNF	British National Formulary
CC	Chronic Constipation
CDDFT	County Durham and Darlington NHS Foundation Trust
CI	Chief Investigator
CPCPH	Centre for Primary Care and Public Health
CRF	Case Report Form
DCC	Durham Constipation Clinic
DMEC	Data Monitoring and Ethics Committee
EC	European Commission
EQ-5D	EuroQol Health Outcome measure
EQ-VAS	EuroQol Visual Analogue Scale
FC	Functional Constipation
FDD	Functional Defecation Disorder
IBS-C	Irritable Bowel Syndrome – Constipation type
GAD7	Generalized Anxiety Disorder Questionnaire
GAfREC	Governance Arrangements for NHS Research Ethics Committees
HT	Habit Training
HTBF	Habit Training Incorporating Direct Visual Biofeedback
HRA	Health Research Authority
ICF	Informed Consent Form

INVEST	Standard Panel of Radio-Physiological Tests of Colonic and Anorectal Function
JRMO	Joint Research Management Office
LTF	Lost To Follow-up
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
PAC-QOL	Patient Assessment of Constipation Quality of Life questionnaire
PAC-SYM	Patient Assessment of Constipation Symptoms Questionnaire
Participant	An individual who takes part in a clinical trial
PCSG	Primary Care Society for Gastroenterology
PCTU	Pragmatic Clinical Trials Unit
PHQ-9	Patient Health Questionnaire -9
PI	Principal Investigator
PIS	Participant Information Sheet
PMG	Programme Management Group
PPIG	Patient and Public Involvement Group
PRO	Patient Reported Outcomes
PSC	Programme Steering Committee
QA	Quality Assurance
QC	Quality Control
QMUL	Queen Mary University of London
QOL	Quality of Life
RAIR	Rectoanal Inhibitory Reflex
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Document Verification
SOP	Standard Operating Procedure
TAI	Transanal Irrigation
TDS	Three Times Per Day
UHND	University Hospital of North Durham
VAS	Visual Analogue Scale
WP	Work Package Signature Page

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND: CHRONIC CONSTIPATION

Constipation is a very common and troublesome symptom in adults across the globe(1)(2)(3)(4). It has an adverse effect on quality of life (5) and incurs significant healthcare costs (6). It is commonly a result of diet and lifestyle factors (for example, inadequate dietary fibre, inadequate fluid intake), medication usage (for example, opiates), or neurological disease (spinal cord injury, Parkinson's, Multiple Sclerosis, stroke).

Where no definite underlying pathology to explain these symptoms can be found, the condition is termed 'functional', 'idiopathic' or 'chronic constipation'. In practice these terms are often used synonymously but for the purpose of this thesis will be referred to as chronic constipation (CC). It remains poorly understood, and there are many interlinked factors potentially contributing to the symptom of chronic constipation including disorders of intestinal motility, disorders of the enteric nervous system/autonomic dysfunction, visceral hyper/hyposensitivity and disorders of the pelvic floor and anorectal musculature (2). Many treatments are available for this condition, ranging from diet and lifestyle measures to pharmacotherapy, biofeedback, trans-anal irrigation and surgical management. The purpose of this chapter is to give an overview of the epidemiology and clinical characteristics of chronic constipation and its current management, as well as providing background to and rationale for, the use of trans-anal irrigation therapy to treat chronic constipation. The nature and aims of the proposed research will also be outlined.

1.2 DEFINITIONS OF CHRONIC CONSTIPATION

There are several different definitions of constipation in the literature. Physicians have tended to focus on frequency of defecation, with less than three bowel motions per week being considered abnormally infrequent(4). However this is often not what patients mean by constipation(4); therefore, factors such as straining, incomplete evacuation, and the passage of hard and/or lumpy stools need to be taken into consideration(2). The Rome III criteria for functional gastrointestinal disorders attempt detailed subdivision of symptoms into distinct disorders; these include Irritable bowel syndrome (constipation-predominant) (IBS-C); Functional Constipation (FC); Functional defecation disorders (FDD) – subdivided into dyssynergic defecation and inadequate defecatory propulsion. The features of these are summarized in **table 1**. These criteria have been updated with the publication of the Rome IV criteria in 2016.

There is evidence of considerable overlap in symptoms between IBS-C and FC and it has been suggested that these may not be distinct and separate conditions(2)(7). The American College of Gastroenterology (ACG) definition of chronic constipation is broader and simpler, and is also widely published. This defines chronic constipation as ‘a symptom-based disorder defined as unsatisfactory defecation characterised by infrequent stools, difficult stool passage, or both, for at least three months’(2). It should be noted that the term ‘chronic constipation’ is not intended to correspond to any particular condition defined according to Rome III, but rather encompasses all three conditions described above.

Constipation is also classified within the literature according to physiological and radiological parameters. Patients may be described as having slow-transit constipation (STC), evacuatory disorders, or a combination of both(8). Some patients describe symptoms of constipation but have normal colonic transit time(8). For this study, the ACG definition given above was used as it is clinically relevant, patient-centred and encompasses a broad range of symptoms of constipation described by patients.

1.3 EPIDEMIOLOGY OF CHRONIC CONSTIPATION

Constipation is a common symptom; a majority of adults will report some degree of constipation at some point during their lifetime. It may be secondary to other disease processes, for example, inadequate dietary fibre, behavioural factors, concomitant medications (for example opioids), diabetes mellitus, neurological conditions, or malignant disease. Where no secondary cause is found, this is termed 'idiopathic', 'functional' or 'chronic' constipation. A recent meta-analysis of adult populations (>= 15 years) suggests chronic constipation has an estimated global pooled prevalence of 14% (1). A further systematic review of studies from Europe and Oceania (3) showed prevalence varying between 5% and 35% (average 17%); prevalence varied widely depending on the definition of constipation used, with self-reported constipation having a higher prevalence. An earlier systematic review of North American populations also found that prevalence was reported highest in studies using self-reporting of constipation symptoms (27% compared with 15-17% if Rome criteria are used)(4).

It has been widely reported that chronic constipation is more commonly seen in women than in men; approximately 17% of female patients in a recent meta-analysis had chronic constipation, compared with 9% of men(1). A review of North American studies found a median female/male ratio of 2.2 (4), while another review reported a mean female/male ratio of 1.78 (3). It has been hypothesized that factors such as hormonal changes, gynaecological surgery and obstetric trauma may contribute to the higher prevalence of constipation in women (9), although this is not fully understood. There is also some evidence to suggest that women have slower intestinal transit overall than men(10), and that they have longer colons(11). Other factors with a modest association with increased risk of chronic constipation include older age and lower socio-economic status (1)(3).

1.4 CHRONIC CONSTIPATION IN SECONDARY CARE

As previously discussed, constipation is common in both men and women in the community, although prevalence varies according to the criteria used to define it. Women are more commonly affected(1). The majority of patients with constipation are managed either by self-medicating or in primary care, by making diet and lifestyle modifications and taking oral laxatives as needed.

However there are some patients whose symptoms are severe and refractory to the aforementioned first-line therapies(12). In these cases, a secondary cause for symptoms (for example; medication, an undiagnosed neurological condition, organic colonic pathology, or psychological morbidity) should be sought. However, there is a definite group of patients

with no underlying cause for their constipation who have a poor response to standard treatment(12). These patients may be referred to specialist gastroenterological clinics for further management of their constipation, and it is in this patient group that further, more detailed, investigations are generally carried out, and different treatment strategies attempted(12). There is also some evidence that patients who see a doctor for their constipation are more likely to report poorer quality of life compared with patients who manage their symptoms themselves(13).

Current evidence suggests that there is a much higher proportion of female patients than male patients in secondary care populations(14)(15), with reported female:male ratios of between 6:1 to 11:1. This gender difference is most pronounced in younger patients (less than 60 years old)(16)(17). This contrasts markedly with the ratio of approximately 2:1 seen in the general population, as described earlier. It has also been reported that female patients in secondary care report significantly reduced stool frequency and significantly more frequent episodes of abdominal pain compared to their male counterparts(18).

There is some evidence that a higher proportion of patients referred to secondary care have pelvic floor dysfunction, rather than slow transit constipation or IBS-C(19). There is also the possibility that patients with pelvic floor dysfunction have a poorer response to laxatives(12) which may contribute to the higher proportion of these patients seen in secondary care compared with primary care. However, this is an unproven association, and the reality is doubtless more complex.

These differences highlight the fact that the patients seen for refractory chronic constipation in secondary care are different from those in the general population or those treated in primary care; it appears that they are more likely to be refractory to treatment with laxatives, have increased likelihood of pelvic floor dysfunction, poorer quality of life, and are disproportionately female.

1.5 PATHOPHYSIOLOGY OF CHRONIC CONSTIPATION

Chronic constipation is classified as a functional disorder, meaning that there is no clearly-described disease process to account for the symptoms reported by the patient(20). Hence, the disease is primarily classified based on patient symptoms, as well as radiological and physiological findings. The Rome III criteria (now superceded by Rome IV) are a frequently-used example of this (see table 1)(21). It has been suggested that using this type of definition leads to heterogeneity within study populations and that this may partly explain why a unifying pathological diagnosis has not yet been found(20).

Nonetheless, several studies have been undertaken to investigate possible causes and risk factors for developing functional gut disorders. Many published studies look at irritable bowel syndrome as a whole rather than chronic constipation specifically; however, much of this research will likely be relevant to both conditions. Proposed pathophysiological factors include inflammatory and neurological factors, genetics, disorders of the gut microbiome, and disturbances in gut motility.

It is worth noting that the subset of constipation patients seen in secondary care generally do not respond as well to correcting lifestyle factors (for example, increasing dietary fibre and fluid intake)(22). This suggests an alternative pathology in this patient cohort compared with patients in the community.

There is evidence of possible inflammatory/neurodegenerative processes that may explain symptoms in some cases. For example, full-thickness biopsies of the jejunum in one study showed several abnormalities in patients with IBS; there was evidence of lymphocyte infiltration of the myenteric plexus, along with neuronal degeneration(20). It is difficult to obtain this information in routine clinical practice, as obtaining full-thickness bowel specimens requires invasive surgery and there are risks of leakage from the biopsy site, with associated complications which may be severe. Additionally, the associations described above are not proven and demonstrating these findings in individual patients may well not lead to better outcomes. It is therefore not practical or desirable to carry this out routinely.

There is also a strong association between risk of developing functional bowel symptoms and enteric infections. One meta-analysis of clinical trials revealed a six-fold increase in risk of developing functional gut disorders after recovering from an enteric infection (23). However, the precise mechanism for this is unknown; it may be related to the inflammation hypothesis alluded to previously(20), with chronic persistent immune activation in the gut leading to abnormal secreto-motor responses and thereby contributing to the patient's symptoms(24) A further association is between joint hypermobility and connective tissue

disorders and gastrointestinal symptoms, including constipation (25), raising the possibility that abnormalities in connective tissue in the intestinal wall may be a factor contributing to symptoms.

Additionally, it has been noted that immunohistochemical staining of intestinal muscle specimens in patients with slow transit constipation reveals a significantly reduced number of Interstitial Cells of Cajal (gut 'pacemaker' cells important in peristalsis and intestinal transit) (26). Colonic motility studies have shown significantly disordered patterns of peristalsis in the colon in patients with functional constipation compared to healthy controls (27), and IBS-D patients exhibit fewer propagating high-amplitude colonic contractions, with correspondingly slower transit(28).

Further research has demonstrated disturbances in gut microflora in patients with IBS, with the nature of this varying depending on patients' symptoms(24). It is known that the gut microbiome plays an important role in healthy gut function, including defence against pathogens, metabolic function, and nutrition(24). Several factors can lead to disruption and alteration of the gut microbiome, including GI infection, surgery, diet, and medications(24), and there is evidence that the composition of the microbiome in constipated patients differs from healthy controls(29)

Genetic factors may also play a role in developing IBS symptoms, although evidence is not conclusive. Although there is some evidence it aggregates in families(24), twin studies have

suggested that genetics play little role where environmental factors are the predominant factor(30). It appears as though genetic factors interact with environmental factors to produce the clinical picture seen in some constipation patients, but that they are not sufficient to explain the disease on their own(24)

Despite numerous associations and hypotheses, a unifying pathophysiology of chronic functional constipation remains elusive. It is likely that a complex matrix of aetiologies is responsible for the symptom profiles seen in each patient. The lack of a definite pathophysiological basis for diagnosis complicates treatment selection, and often a 'trial-and-error' approach is needed, starting with simple, non-invasive therapies and progressing through to more invasive and high-risk treatments if these are unsuccessful. This process is not helped by the lack of availability of diagnostic tests to identify key abnormalities; for example, full-thickness intestinal biopsies are not possible during colonoscopy, and surgical biopsy is high risk and not thought to be ethically acceptable as a routine investigation as described above.

1.6 THE IMPORTANCE OF THE CONDITION

Chronic constipation has a significant economic impact, both through costs of treating the condition and through loss of productivity. One study estimated that 29% of patients with self-reported constipation see a doctor in a 12-month period, with 14% undergoing some sort of diagnostic test(13). When the high prevalence of constipation in the general population is taken into account, as outlined earlier, it is clear that this will lead to significant healthcare costs. It is estimated that the annual direct cost to the Health Service

in the United Kingdom per patient with chronic constipation is £1,700, with a further £3,400 per patient in indirect costs(31). Constipation as a symptom has been reported as incurring Emergency Department costs of US$1.6 billion per annum in the United States, and this appears to be increasing(6). Furthermore, there is evidence that the costs of treatment of functional bowel disorders in secondary care are significantly greater than in primary care(32). It is unclear whether this is due to the disease process itself, or due to the additional costs inherent in secondary care. Nonetheless, if more patients could be treated effectively in primary care then this would reduce costs associated with treating functional bowel disorders.

The impact on productivity is also significant; in a recent study, 51% of employees with chronic constipation had one or more episodes of sick leave, with a mean of 5.2 episodes, mean duration 25.9 days(31). Presenteeism was also a significant problem, with 82% of employees reporting productivity losses at a mean of 161.9 hours(31). A recent Italian study also demonstrated significant losses in productivity due to chronic constipation, with approximately 19% productivity loss and a mean of 2.7 sick days per year due to symptom(33).

Patients with chronic constipation report a significant adverse impact of symptoms on their quality of life(34). one recent study reporting 'extremely/very bothersome' symptoms in 72% of IBS-C patients, 62% of CC patients with abdominal symptoms and 40% of CC patients without abdominal symptoms(5). A review of quality of life in patients with functional

constipation has shown that the impact on quality of life is comparable to that reported for chronic skin diseases, musculoskeletal disorders, and mild asthma(35). It has also been shown that symptom severity correlates with increased adverse economic impact and healthcare resource utilisation(33)(34), and that healthcare utilization correlates with poorer quality of life(13); therefore treating the condition in order to alleviate symptoms has a positive impact not only on patients and their quality of life, but also on healthcare costs and economic productivity.

Patients have reported dissatisfaction both with the effects of their illness on their quality of life and with some health professionals' attitudes to them and their condition (36). There is evidence that some clinicians hold pejorative opinions about patients with functional gastrointestinal disorders (37) and that this is noted by the patients, leading to frustration and discontent from either or both parties(36)(37). The view that the condition is 'all in the mind' can lead to patients being labelled negatively, and patients' feelings of dissatisfaction at not being taken seriously are well described; many feel that a functional diagnosis means their symptoms are not being granted legitimacy in the eyes of the medical profession (36). Psychosocial factors do contribute to symptoms in many cases, both in terms of pre-existing psychological morbidity predisposing individuals to developing functional GI disorders and in the negative impact of bowel symptoms on health-related quality of life, and this aspect of care should be addressed(38). However, dismissing symptoms as entirely psychological has a negative impact on the perceived quality and effectiveness of care(36).

Functional Constipation	Irritable Bowel Syndrome (constipation-predominant)	Functional Defecation Disorder
1) must include two or more of the following: a) Straining >25% defecations b) Lumpy/hard stool >25% defecations c) Incomplete evacuation >25% defecations d) Sensation of anorectal obstruction/blockage >25% defecations e) Manual maneuvers to facilitate >25% of defecations f) <3 defecations per week 2) Loose stools rarely present without laxatives 3) Insufficient Criteria for IBS-C	1) Recurrent abdominal pain for 3 or more days associated with **at least two** of the following: a) Improvement with defecation b) Onset associated with fewer stools c) Onset associated with harder stools 2) Lumpy/hard stools >25% of defecations	1) Criteria for FC met 2) Must have at least two of the following: a) Impaired evacuation (balloon expulsion test or imaging) b) Inappropriate pelvic floor contraction or <20% relaxation basal resting sphincter pressure c) Inadequate propulsive forces 3) **Dyssynergic defecation**: Inappropriate pelvic floor contraction or <20% relaxation of basal resting sphincter pressure with adequate propulsive forces during attempted defecation 4) **Inadequate Defecatory Propulsion**: Inadequate propulsive forces with or without inappropriate contraction or less than 20% relaxation of the anal sphincter

Criteria fulfilled for the last three months with symptom onset at least 6 months prior to diagnosis
FC= Functional Constipation. IBS-C= Irritable Bowel Syndrome (constipation subtype); FDD= Functional Defecation Disorder
Source: Rome III: The Functional Gastrointestinal Disorders (2006)(21)

Table 1: Rome III Criteria for chronic idiopathic constipation

1.7 TREATMENT OF CHRONIC CONSTIPATION

1.7.1 Drug treatments

The mainstay of chronic constipation therapy is drug treatment. Laxatives have a variety of mechanisms of action, including stimulant, softeners, osmotic and bulk-forming. A recent systematic review has found these treatments to be effective in approximately 60% of patients (male and female) with constipation (39). However, as previously discussed, some patients are refractory to treatment with laxatives (12).

Newer agents are now available for the treatment of more refractory cases after laxative therapy has failed to provide adequate relief. Prokinetic agents such as Prucalopride work by increasing colonic propulsion through activation of gut 5-HT4 receptors(40). Placebo-controlled trials have demonstrated a good response rate, with 43-47% of patients reporting an increase in spontaneous complete bowel movements (SCBM), and 24% of patients reporting three or more SCBMs per week(40).

Linaclotide and Lubiprostone are newer laxative treatments that work by increasing colonic secretions. Lubiprostone acts by stimulating chloride channels thereby increasing secretions of intestinal fluid(40). A meta-analysis reported that Lubiprostone is effective in treating refractory constipation when compared to

placebo, with 54.9% of patients reporting a positive response compared with 33.1% in the placebo group, number needed to treat (NNT) = 4 (95% CI 3-7)(39)

Linaclotide causes activation of guanylate cyclase-C receptors on enterocytes, thereby increasing intestinal secretions of chloride and bicarbonate. This leads to increased luminal fluid secretion and increased intestinal transit(12). This treatment has also been shown to be effective in chronic constipation, with a positive response to treatment reported in 20.1% of study participants compared with 5.1% in the placebo group, NNT = 6 (95% CI 5-8)(39)

1.7.2 Habit Training and biofeedback

Habit training and biofeedback involve adjusting patients' behaviours in order to achieve more effective defecation. Habit training incorporates advice regarding toilet routine, posture, breathing exercises, and answering the 'call to stool'. Biofeedback is a more formal assessment of anorectal function by objectively measuring pressures and muscular co-ordination. This enables the patient to re-train their defecatory muscles in order to achieve more effective defecation. The goal of biofeedback therapy in chronic constipation is to enable patients to increase their defecatory propulsive force by enabling greater coordination of increasing abdominal and intra-rectal pressures, and synchronized relaxation of the anal sphincters and pelvic floor(41). It incorporates verbal, nurse-led instructions in conjunction with visual representations of the relevant pressures, measured through

electromyography (EMG). Other forms do not make use of EMG and employ verbal feedback and/or balloon pressure feedback.

Regarding its role in the treatment of chronic constipation, a meta-analysis has suggested that biofeedback is superior to non-biofeedback, although there was no significant difference between EMG and non-EMG feedback(42). A recent Cochrane review(43) found biofeedback to be superior to laxatives and 'sham' biofeedback for the treatment of chronic constipation. However the studies included in both reviews were of low methodological quality due to small sample sizes (a mean sample size of 48 patients in the Cochrane review), heterogeneous or poorly-defined demographics and symptom profiles of participants, and inconsistency both of the intervention and the outcome measures used between studies(43). There is some disagreement in the literature regarding the effectiveness of biofeedback in dyssynergic defecation compared with slow transit constipation, with some evidence indicating that it is significantly more effective for patients with dyssynergia(41)(44). However, other research had demonstrated improvement in intestinal transit as well (45).

1.7.3 Trans-Anal Irrigation Therapy

Trans-anal irrigation therapy (TAI) is in widespread use throughout the UK as a treatment for bowel dysfunction. It has been used successfully to treat adults and children with neurogenic constipation(46)(47)(48), and faecal incontinence(49). However, evidence for the use of trans-anal irrigation therapy for chronic functional

constipation in adults is not universally acknowledged; this will be covered in detail in the next chapter.

Two alternative systems for delivery of trans-anal irrigation exist; low-volume systems delivering approximately 70ml per irrigation, and high-volume systems delivering up to 2 litres of irrigation (although typically only 0.5 – 1.5 litres is required per irrigation). The low-volume system is cheaper, costing approximately £750 per patient per annum based on alternate-day use, compared with approximately £1200-1900 for high-volume irrigation, and may be more acceptable to patients.

Trans-anal irrigation has been shown to be a low-risk intervention and is widely used in a variety of defecatory disorders. Serious adverse events are rare, with one study reporting 2 non-fatal bowel perforations out of approximately 110,000 irrigation treatments(49). Other potential side effects include pain, bleeding, painful haemorrhoids and anal fissure. Minor reversible side effects are relatively common, with one study reporting 74% of users experiencing some form of adverse event over the course of the treatment(50).

1.7.4 Surgical treatment

Several operations have been proposed to treat chronic constipation surgically. However, this is generally seen as a treatment of last resort, because the outcomes of such surgery can be highly variable and the risks of complications are often significant. The multifactorial nature of the illness and its complex and incompletely-understood pathophysiology are likely to be significant factors contributing to this. It is important that all patients offered surgical intervention are fully aware of the possible risks, the potential for failure of therapy and also that they are carefully matched to the correct procedure.

Formation of a loop ileostomy, in which a loop of distal small bowel is exteriorized and the stool collected in a bag, has been well described. This can be effective for the relief of symptoms, however it is associated with complications and morbidity(51). Some patients have persistent constipation despite the ileostomy; the reasons for this may be due to the systemic neuromuscular abnormalities implicated in the pathophysiology of chronic constipation, as outlined previously.

Resection of the colon and either joining the small bowel to the rectum (total colectomy with ileorectal anastomosis) or leaving an end ileostomy has also been suggested as a therapeutic option in cases of refractory constipation (52). However, one study of 40 patients reported successful treatment in only 75% of cases, with a postoperative complication rate of 20% (52).

An alternative surgical approach is the creation of an appendicostomy to allow antegrade irrigation of the colon. This is known as an antegrade continence enema (ACE procedure). Initially described in children(53), it has become established in the treatment of adults with both faecal incontinence and constipation(54)(55). This procedure has the advantage of being more reversible than the other techniques described, and the surgery is generally less radical as no major bowel resection or anastomosis is undertaken. However, outcomes are variable with a successful outcome in approximately 74% of patients in one study(56). This study also reported surgical complication rates (all complications) of 38%, although this includes patients with a colostomy and neo-appendicostomy as well as appendicostomy only.

In patients where obstructive defecation symptoms predominate, and where a significant structural abnormality is felt to be contributing to this (for example, recto-rectal intussusception, rectocele or rectal prolapse), a Laparoscopic Ventral Rectopexy can be considered. This procedure leads to surgical correction of structural defects in the pelvic floor and has been shown to be effective when used in appropriately selected patients(57).

Overall, the evidence for effective treatments for CC is weak, leaving clinicians with a care pathway approach based on trial and error which is both costly and places the patient at high risk of adverse events. Therefore the case for developing an evidence based care pathway is clear and urgent. Thus, funding was granted by the National Institute for Health Reaearch (NIHR) as a programme grant to conduct a research programme to evaluate several treatments highlighted above, The CapaCiTY programme, outlined below.

1.8 THE CapaCiTY PROGRAMME

The Chronic Constipation Treatment Pathway (CapaCiTY) programme is a series of interlinked clinical trials and qualitative enquiry aiming to evaluate the effectiveness of a series of treatments for chronic constipation (Biofeedback and habit training, anal irrigation, and laparoscopic ventral rectopexy surgery), in order to develop an evidence-based treatment algorithm for patients with chronic constipation. It consists of three interlinked studies running in parallel. These results will be analysed and combined to create the treatment algorithm. CapaCiTY study 2, within which this MD thesis is nested, is the study of anal irrigation therapy, recruiting from September 2015 until October 2018, at approximately 10 sites across the United Kingdom.

1.9 AIMS AND SCOPE OF THE STUDY

As previously outlined, there are several areas where our understanding of chronic constipation is limited and where further research is required. In particular, the CapaCiTY 02 study aims to provide high-quality evidence for the use of trans-anal irrigation therapy in chronic constipation. It attempts to evaluate not only the comparative efficacy of high-volume and low-volume irrigation, but also to evaluate the impact of tailoring therapy to individual patients based on patient-reported experiences and on radio-physiological investigation results. This will allow a far more detailed assessment of the role of irrigation therapy in this patient group than that which is currently available.

In this thesis, a systematic review of the current evidence for trans-anal irrigation in chronic constipation will be presented in order to assess the strength of the current evidence base for this treatment. Also, the quantitative data from the first patients recruited to CapaCiTY 02 at the University Hospital of North Durham will be presented with the aim of evaluating the feasibility of performing this study as per protocol, both at this site and at other sites in England.

Additionally, qualitative interviews with selected study patients will enable an understanding of the patients' experiences of using irrigation therapy. These data will complement the quantitative study by exploring patients' lived experience of learning, using, and continuing irrigation.

CHAPTER 2: TRANS-ANAL IRRIGATION THERAPY TO TREAT ADULT CHRONIC FUNCTIONAL CONSTIPATION: SYSTEMATIC REVIEW AND META ANALYSIS

2.1. INTRODUCTION

Before describing the methods used to conduct this feasibility study, it is necessary to examine in detail the current evidence for the use of trans-anal irrigation therapy in chronic constipation. The following chapter will describe a systematic approach to reviewing the literature, as well as providing the results of a meta-analysis of currently-published trials on this topic. This chapter has been published in a peer-reviewed journal (Appendix III, page 308).

2.1.1 Rationale and aims

Trans-anal irrigation therapy has become established as a treatment for neurogenic constipation(47), and it has also been described as a useful therapy for functional constipation(49). It is generally safe, with a very low incidence of serious complications(58). Therefore it has been chosen for evaluation as part of the Chronic Constipation Treatment Pathway (CapaCiTY) programme in patients whose constipation is refractory to laxatives and nurse-led behavioural therapies. The aim of this chapter is to summarise and critically evaluate the current evidence for the use of trans-anal irrigation in chronic functional constipation in order to inform the development of a feasibility study for a randomised controlled trial.

2.1.2 Trans-anal irrigation

Trans-anal irrigation involves instilling tap water into the rectum via the anus, using either a balloon catheter or cone delivery system. This is attached via a plastic tube to an irrigation bag holding up to 2 litres of water; alternatively a low-volume system

consisting of a hand pump and a cone may be employed. Patients vary in the frequency and volume of irrigation depending on their response to treatment; typically, irrigation is used 2-3 times per week. The low-volume system is cheaper, and may be more acceptable to patients. It is not known which system is more effective.

Proposed mechanisms of action include simple mechanical washout, colonic movement stimulated by the washout, or a combination of these(49). However, evidence for the use of trans-anal irrigation therapy for chronic functional constipation in adults is not universally acknowledged, and there are questions about long-term benefit(58).

A review of current evidence for irrigation was undertaken, and is now published(59) (see appendix 3) to define what is known about this treatment as well as to identify areas where evidence is lacking and further research is required.

2.1.3 Research question

What is the strength of the evidence for trans-anal irrigation therapy for chronic functional constipation, with reference to effectiveness, safety and methodological quality of studies?

2.2. METHODS

2.2.1 Eligibility criteria

Primary research articles that include patients with chronic functional constipation as defined above, treated with retrograde trans-anal irrigation at home as

outpatients, and published in English in indexed journals were eligible. The following were not eligible for inclusion: articles solely studying patients with a known cause for their constipation (e.g. neurogenic constipation, opioid-induced constipation, other organic cause); conference abstracts, audits, letters and commentaries; articles studying antegrade irrigation (a very different treatment involving the surgical creation of an appendicostomy) *(Table 1)*. Reviews were not included but relevant review articles(49)(10) were screened for further relevant studies, as were citations of retrieved studies. No protocol was registered, however the review was reported in accordance with the PRISMA statement (2009)(61).

Table 1: Inclusion and exclusion criteria

Inclusion	Exclusion
Primary research	Audit/letters/commentaries/opinion/review articles
Patients with Chronic Functional Constipation (Obstructive defaecation and/or slow transit/IBS-C)	Studies in children (<18 years) only
Full articles published in peer-reviewed journals	Studies in neurogenic constipation only
English Language	Studies where all patients have undergone colorectal surgery (resection or rectopexy, etc.)
Retrograde irrigation using standard equipment performed at home	Studies in stoma patients only
Primary outcome is patient symptom improvement/response to treatment	Studies in antegrade irrigation only

2.2.2 Search strategy

The following databases were systematically searched through Ovid Online:

- **"All EBM Reviews"** (comprising: Cochrane Database of Systematic Reviews (2005 to March 2015), ACP Journal Club (1991 to March 2015), Database of Abstracts of Reviews of Effects (1st Quarter 2015), Cochrane Central Register of Controlled Trials (March 2015), Cochrane Methodology Register (3rd Quarter 2012), Health Technology Assessment (1st Quarter 2015), NHS Economic Evaluation Database (1st Quarter 2015));
- **Embase** (1974 to 2015 Week 15);
- **Ovid MEDLINE(R)** (1946 to April Week 2 2015).

The following search terms were used (searched in 'all fields'): "bowel dysfunction"; "defaecation."; "defecation"; "constipation"; "irrigation". The Boolean Operators "AND" and "OR" were used to combine these terms appropriately and refine the search (table 2). The search was limited to English language articles and to studies in humans.

Abstracts and citations were screened by one researcher (CDE) and potentially relevant articles were retrieved. Articles that fulfilled the inclusion criteria were included in the review. Reference lists of eligible articles were searched to identify potentially relevant articles missed by the original database search. Another researcher (Dr Helen Close) reviewed 10% of the citations and abstracts, as well as 100% of the full-text articles, to confirm appropriate implementation of the eligibility criteria and accuracy of data extraction. For practical and resource reasons a grey

literature search was not performed, as the likelihood of finding appropriate studies not identified in retrieved citations or reviews was considered very small.

Table 2: Search of bibliographic databases

Number	Searches	Results
1	Constipation.af*	90438
2	Bowel dysfunction.af	2264
3	Defecation.af	25606
4	Defaecation.af	1921
5	Irrigation.af	55773
6	1 OR 2 OR 3 OR 4	110886
7	5 AND 6	517
8	Limit 7 to English language	452
9	Limit 8 to Humans	405
10	Remove Duplicates from 9	**292**

* af: all fields (includes Subject headings and all test fields)

2.2.3 Data collection

Data were extracted from eligible studies using standardised data collection forms. Data items included study methodology, patient information (including demographic details and definition of 'constipation' used), primary outcome data (including follow up period), duration of use of treatment, and adverse events reported. The Cochrane assessment of bias for non-randomised studies tool (ACROBAT-NRSI) (62) was used to evaluate methodological quality and sources of bias for the included studies.

2.2.4 Outcomes

The primary outcome was the proportion of patients with an investigator-reported positive outcome to trans-anal irrigation therapy.

Secondary outcomes included response by constipation type, duration of treatment use and safety of treatment assessed by adverse event reporting in studies.

2.2.5 Analysis

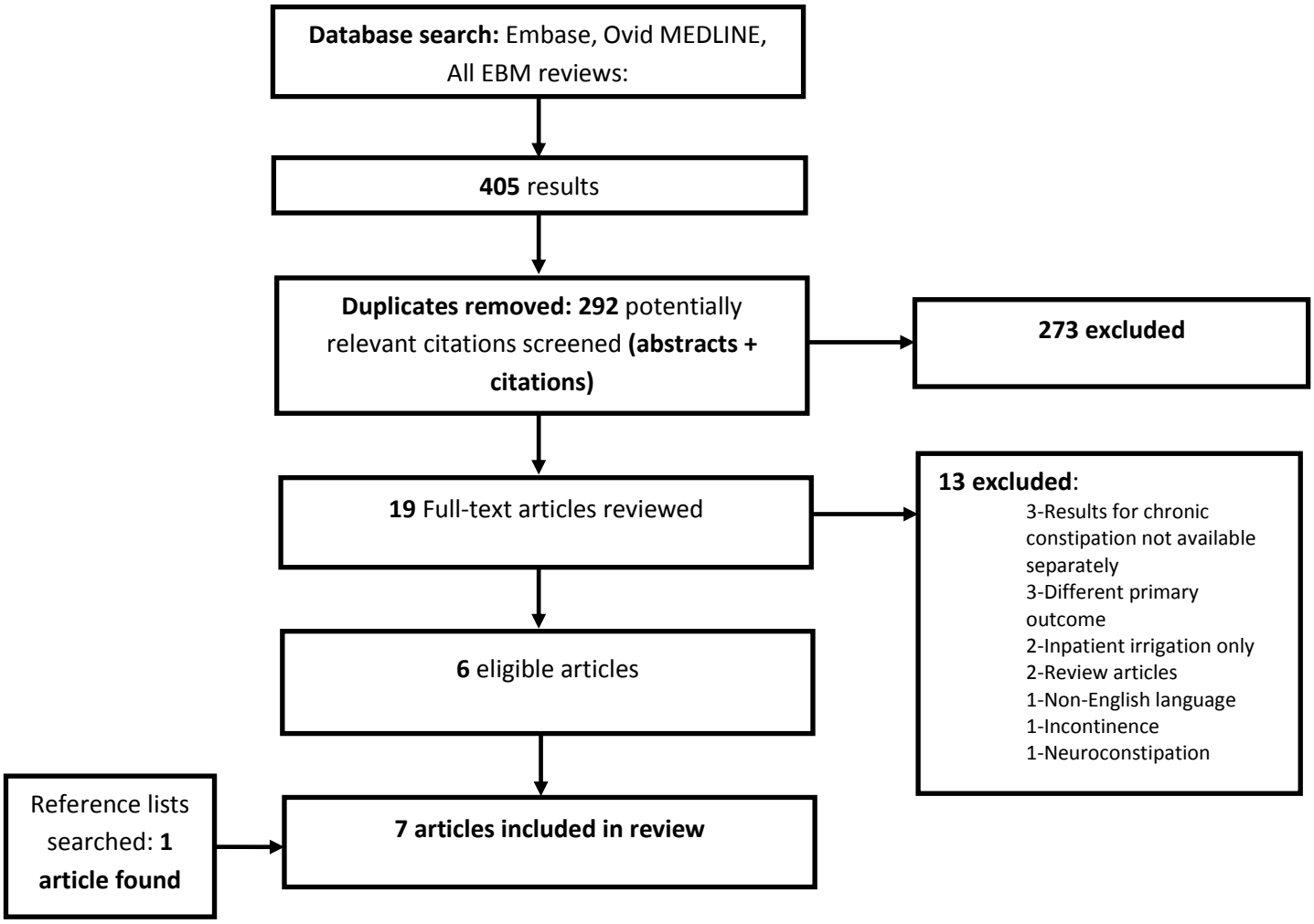
Both qualitative review of study results and quantitative analysis was performed. Rates of complications are reported and statistical pooling of proportion estimates was explored using fixed and random effect models within StatsDirect © Version 3. Both Q and I^2 statistics were calculated to assess study heterogeneity. An Egger test was performed to assess risk of publication bias.

2.3. RESULTS

Of 292 abstracts and citations reviewed, 19 full-text articles were retrieved. Of these, six were suitable to be included in the review(58)(63)(64)(65)(50)(17). Reference lists of these articles were reviewed and a further eligible article was identified(18), giving a total of 7 articles (Figure 1). All eligible studies reported outcomes using high-volume irrigation only. One further study using low-volume irrigation was found, not reporting constipation-specific outcomes and was excluded from the final analysis(68). Studies identified were prospective cohort studies, or retrospective, uncontrolled case series from European nations (Table 3). In each

study the patient case mix included patients with faecal incontinence, soiling and following colorectal surgery. However the articles reported outcomes separately for each group, making it possible to evaluate outcomes for chronic functional constipation. Reported mean duration of therapy varied from 8 months to 102 months (range 1-216 months across studies).

Figure 1: PRISMA flowchart



Studies were small, with an average number of patients per study of 36 (range 10-79); there was no evidence of a power calculation being performed for any study.

2.3.1 Outcome of anal irrigation therapy

Patient-reported satisfaction, either subjective or using a visual-analogue scale, was the outcome most commonly reported (5 studies) (13)(15)(16)(17)(18). One study used resolution of symptoms as the outcome measure(64), another used a combination of patient-reported symptom improvement and ongoing use of treatment(58). If a patient died while still using the treatment this was also considered successful. One study(63) reported both patient-reported satisfaction and change in Cleveland constipation score as markers of treatment success; the patient-reported satisfaction outcome was included in this analysis as it enabled meaningful comparison with other studies.

Table 3: Study characteristics

Study	Design and methods	Level of evidence*	Definition of constipation	Definition of successful treatment
Chan (63)	Prospective cohort study	III	Infrequent passage of stool +/- straining/ digitation/ incomplete emptying	i) Improvement in Cleveland Constipation Score ii) Patient-reported satisfaction
Christensen (58)	Retrospective questionnaire survey and case note review	III	Idiopathic constipation including slow transit, obstructed defecation and 'undetermined'	i) Ongoing use ii) Resolved symptoms iii) Still using irrigation at time of death
Koch (64)	Prospective cohort study	III	<2 bowel motions per week, straining or incomplete evacuation >50% motions in previous year	Resolution of incomplete emptying or straining symptoms
Cazemier (65)	Retrospective case series questionnaire survey	III	Constipation according to Rome II criteria	Patient-reported satisfaction
Gosselink (50)	Retrospective case series, questionnaire survey	III	Obstructed defecation based on; straining, incomplete evacuation, digitation, fullness, <3 motions/ week	Patient-reported satisfaction
Gardiner (67)	Case series; not stated if prospective or retrospective	III	Obstructive defecation and slow transit (?which criteria used)	Patient-reported satisfaction
Crawshaw (66)	Retrospective case note review and questionnaire survey	III	The inability to evacuate the rectum when desired (includes obstructed defecation and dyssynergic defecation)	10mm increase on VAS (10% improvement)

** Eccles, Mason 2001 How to develop cost-conscious guidelines*(69)

Studies report variable response rates to therapy (table 4). The proportion of patients who had a positive outcome to therapy varied from 30% (64) to 65% (63)(50). Overall, 254 patients with chronic functional constipation were included in studies, with 128 having a positive response to irrigation therapy (Table 4).

A fixed effect analysis of proportions gave a pooled response rate of 50.4% (95%CI: 44.3% to 56.5%). Although there was no evidence of publication bias (Egger: bias = 0.259, p=0.91), there was evidence of substantially heterogeneity between studies (Q[6]=18.2, p=0.0057; I^2=67.1%). A random effects estimate was similar, if less precise: 50.9% (95%CI: 39.4% to 62.3%), (see Figure 2).

Four studies reported results for different sub-types of constipation. Sample sizes in all studies were very small (10 – 37 patients with OD) and differences between sub-groups remain anecdotal. When results from all four studies where results for different types of constipation are reported are combined, there was no consistent pattern of outcome between subtypes. Methodological weaknesses, inconsistencies in outcome measures and small sample sizes limit meaningful comparison.

2.3.2 Safety of anal irrigation therapy

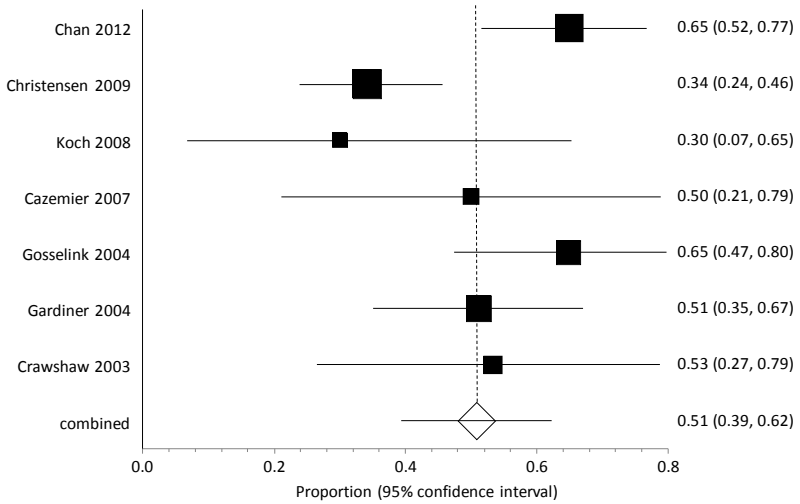
The most clinically significant risk associated with irrigation is bowel perforation. Only one study reported this complication(58) and this occurred in two patients. If reliably reported this, represents 2 perforations in approximately 110,000 irrigations, or less than 0.002% risk per irrigation. No studies reported mortality associated with irrigation. Studies were inconsistent in their reporting of adverse

Table 4: Demographics and overall response to treatment

Study	Patients with Chronic Constipation (n)	Average age (Years)	Male:Female	Positive response n(%)	Time to assessment (Months (range))	Duration of therapy (Months (range))
Chan (63)	60	46	8:52	39 (65)	6*	10.7*
Christensen (58)	79	52*	25:62*	27 (34)	21 (1-116)*	8 (1-85)*
Koch (64)	10	55.4	4:7*	3 (30)	3*	-
Cazemier (65)	12	46	1:3	6 (50)	-	102 (30-216)*
Gosselink (50)	37**	54	5:32	24 (65)	56 (8-154)*	[++]
Gardiner (67)	41	-	-	21 (51)	-	-
Crawshaw (66)	15	54 (41-61)*	13:35*	8 (53)	12*[+]	-
Total	**254**	-	-	**128**		

- Data not available
**Whole cohort*
***Obstructed Defecation only*
[+] Inferred from study report
[++]Not stated, but 73% of patients still using TAI at 30 months

Figure 2: Proportion meta-analysis plot [random effects]



Plot illustrates the proportion of positive responders in each study, along with the combined positive response rate and weighted average (diamond and dotted line)

events and the level of disaggregation between pathologies treated, thus only a narrative summary is possible.

Minor and self-limiting adverse events were commonplace in studies but may to some extent have been tolerated by patients, with up to 74% of long term continuing users reporting some form of related and expected adverse events in one study(50). The most commonly-reported adverse events included abdominal cramps/discomfort (33-40%) (65)(58)(50); anorectal pain (5-25%)(58)(50); anal canal bleeding (1-20%)(58)(63); leakage of irrigation fluid (30-75%)(58)(50); and expulsion of the rectal catheter (39%) (58). One study reports a 43% incidence in 'technical problems' with irrigation(50). In one study, 28% of those discontinuing therapy gave side effects or technical issues with irrigation as a reason for discontinuing(58).

Therefore, whilst one or more side effects were experienced by a large proportion of patients undergoing anal irrigation, the risk of major life-threatening, life-limiting or irreversible complications was very low.

2.3.3 Methodological quality

Generally, the studies were of weak methodology. There were no randomised controlled studies or case-controlled studies and most articles were retrospective questionnaire and case note based case series (Table 3). Two studies (63)(64) were prospectively designed with fixed follow up points, but numbers were relatively small (only 60 and 11 chronic functional constipation patients respectively). A further study(67) did not state whether data collection was prospective or retrospective.

Risk-of–bias assessment suggests that five studies were at serious risk of bias, and the other two were at moderate risk (Table 5). The retrospective questionnaire-based studies also suffered from non-response to surveys and missing data. This is likely to lead to bias and the results must be interpreted in light of this (i.e. were responders significantly more or less likely to have responded well to irrigation therapy?). Given the limitations of design and size, available studies are unable to provide robust evidence for the treatment effect of trans-anal irrigation.

Patient heterogeneity was also an issue. One study included both children and adult patients together (58) and the proportion of children was not reported. Neither was it stated whether there was a difference in outcome between the adults and children. One study(65) included three patients with neurological problems in its constipation cohort, representing 25% of this study population. As neurogenic constipation may respond differently to irrigation(70), this may have affected the results. A further study included 5 patients out of 11 with chronic constipation who had had colorectal surgery (one resection and four rectopexies)(64). Another study(66) also included patients who had undergone pelvic surgery or rectopexy in the chronic constipation cohort. It is not known precisely what effect these inclusions had on response to treatment but these remain a potential source of confounding.

Table 5: Risk of bias assessment

Study	Risk of bias by type							
	Confounding	**Selection**	**Measurement of interventions**	**Performance**	**Missing data**	**Measurement of outcomes**	**Reporting**	**Overall**
Chan (63)	Moderate	Low	Low	Low	Moderate	Moderate	Low	**Moderate**
Christensen (58)	Moderate	Moderate	Moderate	No information	Low	Serious	Low	**Serious**
Koch (64)	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Cazemier (65)	Serious	Serious	Serious	Low	Low	Serious	Low	**Serious**
Gosselink (50)	Low	Serious	Moderate	Low	Moderate	Serious	Low	**Serious**
Gardiner (67)	No information	No information	Moderate	No information	Low	Serious	No information	**Serious**
Crawshaw (66)	Moderate	Serious	Serious	Low	Serious	Serious	Low	**Serious**

2.4 DISCUSSION

This review brings together the findings of seven primary research studies which examine outcomes of trans-anal irrigation therapy in patients with chronic functional constipation.

Studies retrieved are small and not of robust methodological quality; only two are prospectively-designed, and there is the potential for reporting bias in the four studies that use questionnaires. This finding underlines the fact that the evidence for use of irrigation in functional constipation is currently weak.

The aggregate success rate of irrigation therapy is around 50% based on these seven studies. Given the chronic and refractory nature of the symptoms in many of these patients this may be considered adequate, especially given the simple and reversible nature of the treatment(49). By comparison, response rates for drug treatments in this group of patients has been reported as 20-40%, though these are prospective RCTs reporting symptom based primary end-points(71)(72)(73). Additionally, reported response rates in neurogenic constipation are only slightly higher – around 60% (5). Mean duration of use of treatment was reported between 8 months and 102 months. Inconsistencies in reporting findings, methodological differences and weak study design mean that there is insufficient evidence to state with any confidence exactly what the duration of benefit of treatment should be.

The majority of patients experience some form of adverse event although these are mostly minor, reversible and self-limiting. This may be a factor in determining the

success of therapy: the need for high levels of patient motivation, as well as support from specialist nurses, is recognised(49). The rates of life threatening complications are very low throughout the studies: Irrigation can be considered a safe therapy, when used with proper training. Since this systematic review was carried out, a global audit of bowel perforations related to trans-anal irrigation has been published and this reports a rate of perforation of 2 perforations per 1 million irrigations, with higher risk in the first 8 weeks of therapy(74).

There is insufficient evidence to state with any certainty how best to tailor therapy to patient symptoms. A recent review based on expert consensus(75) has proposed a number of regimes to overcome problems with irrigation and so improve outcomes, but experimental trial evidence is lacking, especially for functional constipation patients. In spinal cord injured patients, it has been found that emptying the rectosigmoid using irrigation stimulates colonic transit(75) however it is not clear whether this is transferable to patients with slow colonic transit and functional constipation. Scintigraphic studies have suggested that these patients have a different response to irrigation, with reduced colonic clearance compared with spinal cord injured patients(70). In addition, none of the studies assess outcomes of low-volume anal irrigation systems.

Two previous systematic reviews examining trans-anal irrigation were found(49)(60). These reviews, while valuable, have several limitations: They focus on irrigation as a therapy for several conditions including neurogenic constipation, faecal incontinence, idiopathic constipation and mixed symptoms; also, one review (10) incorporates studies of inpatient pulsed irrigation which is a very different therapy

from home irrigation described in this review. The findings of this review are similar to the previous studies with respect to the weak nature of current evidence and the heterogeneity of the studies included. Subsequent to these reviews further studies have been identified and this review is the first to address irrigation therapy in idiopathic constipation only. This is also the first systematic review on this topic to be conducted in accordance with the PRISMA statement. Additionally, this is the first meta-analysis of the effectiveness of irrigation in chronic functional constipation.

2.5 CONCLUSION

This review suggests that trans-anal irrigation may be an effective therapy for chronic constipation, and may be considered in patients who have not responded to medical management. Irrigation is safe and its effectiveness is at least comparable with pharmacological therapies. However, the evidence to guide its use in chronic functional constipation is weak, and its long-term benefits are unclear. There are no reported data on cost-effectiveness of irrigation: whether treatment provides good value for money from scarce health service resources. There is a clear need for well-designed prospective trials to evaluate the effectiveness, duration, and adverse consequences of treatment, as well as to assess how best to tailor therapy to individual patients. Future studies should have defined outcome measures, for example improvement in validated quality-of-life questionnaires within a defined time point. More evidence about the comparative effectiveness and cost-effectiveness of low-volume and high-volume irrigation systems would also be valuable. The quantitative and qualitative components of the CapaCiTY 02 study aim

to address the gaps highlighted by this review. The methodology employed will be outlined in the next chapters.

CHAPTER 3: QUANTITATIVE STUDY METHODOLOGY

3.1 INTRODUCTION

This chapter aims to set out the methods used in the quantitative arm of the study. The trial overview, design and follow-up procedures will be described, as well as a detailed overview of what was done at each study visit. Ethical considerations, as well as safety and data protection aspects will also be discussed.

3.2 RATIONALE AND OVERVIEW OF STUDY DESIGN

3.2.1 Rationale for conducting the Chronic Constipation Treatment Pathway (CapaCiTY) 02 study

As previously noted, there is a need for more robust evidence to evaluate the effectiveness of irrigation therapy for chronic functional constipation, and the CapaCiTY 02 study has been designed to provide this. It has also been designed to compare the effectiveness of the two different anal irrigation systems (high volume and low volume), as there are currently no data demonstrating superiority of one system over the other. Given the differences in cost between the two systems, a randomised study of well-characterised patients comparing the two methods would provide useful information on whether one system holds a clear advantage over the other. In addition, the short- and long-term efficacy and acceptability of therapy in chronic constipation requires evaluation. This is timely and informative given the rapidly increasing popularity of this treatment and the fact that anal irrigation is an invasive therapy for which patient selection should be optimised to maximise benefit.

3.2.2 Relationship between the MD study and CapaCiTY 02

The CapaCiTY 02 study will run for 5 years at approximately 10 centres across the UK. This thesis is nested within this study, and reports the results from a single centre (University Hospital of North Durham) over one year of recruitment. This study was conducted as per the CapaCiTY 02 protocol and should be considered a feasibility study, aiming to evaluate the appropriateness and feasibility of implementing the CapaCiTY 02 study locally, as well as highlighting potential problems and solutions to inform the implementation of a full multi-site trial. The aims of this thesis are set out below, as are the objectives for the CapaCiTY 02 study overall.

3.3 TRIAL OBJECTIVES

3.3.1 Thesis/ MD study objectives

1. To determine the feasibility of performing this study as per protocol at a single site and to identify/anticipate problems and solutions to efficiently deliver the study at other sites.
2. To determine willingness of patients to participate in this study, and to estimate the likely recruitment rate and whether the calculated sample size is achievable within the study timeframe.
3. To determine follow-up rates, compliance and response rate to outcome measures (questionnaires, diaries).

4. To provide a descriptive analysis of initial trial outcome data. This will include an estimate of the standard deviation of the primary outcome measure for CapaCiTY 02 (see below).

3.3.2 CapaCiTY 02 Study Objectives

Primary Objective

1. To compare the impact upon patient disease specific quality of life of transanal irrigation initiated with a low-volume versus high-volume system in patients with chronic constipation, measured at 3 months.

Secondary objectives

To determine:

1. Disease specific outcomes at 3, 6 and 12 months.
2. Survival (continuation of benefit) and acceptability by type of system and for the whole cohort
3. The influence of patient characteristics (urge to defecate, balloon sensory testing results) upon treatment success, and response by type of system used.
4. The acceptability of each system to patients.
5. Strategies for tailoring therapy to meet patients' individual needs, and the factors involved in this.
6. The safety of each system and prospective tracking of adverse events (AEs)

3.3.3 Endpoints

Clinical endpoints

All clinical endpoints were recorded at baseline, 3 and 6 months in face-to-face clinics (or by telephone call if necessary). PAC-QOL, PAC-SYM and EQ-5D-5L, EQ-VAS were additionally collected at 1 month; this was to capture reasons for early non-response to therapy, as well as to better characterise the patients group and provide more data for economic analysis. The analysis of the primary endpoint was at 3 months. Further follow up and outcome data collection (up to 12 months) will be conducted as part of the CapaCiTY 02 trial but these results are not included in this thesis.

Primary Clinical Endpoint

- Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL(76)) at 3 months.

Secondary Clinical Endpoints

- PAC-QOL score and individual domain scores.
- Time to cessation of each system of irrigation; total time in treatment with either system.
- Reason for cessation (of each system).
- Patient Assessment of Constipation Symptoms (PAC-SYM)(77): aggregate and domain scores.
- Irrigation journal: volume and duration of irrigation.
- Number and nature of bowel motions captured in patient diary.

- Symptom scores derived from diary records (taken over two weeks before or around each follow-up contact. These included number of spontaneous complete bowel motions.
- Generalized anxiety disorder questionnaire (GAD7)(78).
- Depression, anxiety and somatisation modules of the PHQ-9(79).
- Global patient satisfaction / improvement score (VAS).
- Patient recommendation to other patients.
- Behavioural response to illness questionnaire (CC-BRQ), and brief illness perception questionnaire BIPQ (CC)(80).
- Generic quality of life: EuroQol (EQ-5D-5L and EQ-VAS) scores(81).
- Patient acceptability.
- Use of healthcare resources, adverse events, and concomitant medications collected using patient journal.

3.4 OVERVIEW OF STUDY DESIGN

The study is a two-arm, randomized controlled trial comparing high-volume (HV) with low-volume (LV) anal irrigation. Eligible patients were consented for participation before undergoing a series of radiological and physiological investigations (X-ray colonic transit study, anorectal physiology testing, referred to hereafter as 'INVEST') and were then randomized 1:1 to either the HV or LV group. Patients were trained in their allocated system by experienced health professionals (irrigation nurses). Patients were followed up at 1, 3 and 6 months (or until they elected to discontinue therapy). After three months of using their allocated system,

patients could switch to the other system to see if that was more effective. Participants will continue with follow up to 12 months as part of the CapaCiTY 02 study. Follow-up up to 6 months will be reported within the MD (feasibility study) timeframe.

3.4.1 Inclusion Criteria

- Age 18-70 years.
- Patient self-reported problematic constipation.
- Symptom onset > 6 months before recruitment.
- Symptoms met American College of Gastroenterology definition of constipation(2).
- Constipation failed treatment to a minimum basic standard (NHS Map of Medicine 2012) (lifestyle AND dietary measures AND≥2 laxatives or prokinetics) tried (no time requirement)
- Ability to understand written and spoken English (due to questionnaire validity).
- Ability and willingness to give informed consent.
- Failure of previous nurse-led behavioural therapy.
- Ability of patient/carer to use anal irrigation.

The study used the American College of Gastroenterology definition of constipation(2) which is reasonable, simple and extensively published: unsatisfactory defecation characterized by infrequent stool, difficult stool passage or both for at least previous 3 months.

3.4.2 Exclusion Criteria

The study interventions necessitated the exclusion of major causes of secondary constipation. In detail;

- Significant organic colonic disease (including undiagnosed/un-investigated 'red flag' symptoms); IBD; megacolon or megarectum (if diagnosed beforehand) [the study will provide a useful estimate of the prevalence of such cases in referral practice]; severe diverticulosis/stricture/birth defects deemed to contribute to symptoms (incidental diverticulosis not an exclusion).
- Major colorectal resectional surgery.
- Current overt pelvic organ prolapse (bladder, uterus, vagina, rectum) or disease requiring surgical intervention.
- Previous pelvic floor surgery to address defecatory problems: posterior vaginal repair, STARR and rectopexy; previous sacral nerve stimulation.
- Previous use of transanal irrigation therapy to treat constipation (Note: this does not include private 'colonic irrigation' in the community/complementary therapy setting)
- Rectal impaction (as defined by digital and abdominal examination: these form part of the NHS Map of Medicine basic standard).
- Significant neurological disease deemed to be causative of constipation e.g. Parkinson's, spinal injury, multiple sclerosis, diabetic neuropathy (not uncomplicated diabetes alone).
- Significant connective tissue disease: scleroderma, systemic sclerosis and SLE (not hypermobility alone).

- Significant medical comorbidities and activity of daily living impairment [based on Bartel index(82) in apparently frail patients, Bartel index <=11].
- Physical disability/impairment which prevented use of one or other of the irrigation devices.
- Major psychiatric diagnosis [schizophrenia, major depressive illness, mania, self-harm, drug/alcohol addiction].
- Chronic regular opioid use (at least once daily use) where this was deemed to be the cause of constipation based on temporal association of symptoms with onset of therapy; all regular strong opioid use.
- Pregnancy or intention to become pregnant during study period.

3.5 STUDY DESIGN PLAN/STUDY VISITS

3.5.1 Setting

The Durham Constipation Clinic is a specialist tertiary referral clinic based at the University Hospital of North Durham, accepting referrals from across Northern England (including Northumberland, Tyne and Wear, County Durham, Teesside, Cumbria and Yorkshire). It has been running for over 15 years and provides a holistic, multi-disciplinary service to patients with chronic constipation. Research is integral to the aims of the service, which is focussed on furthering understanding of, and improving therapy for, this very difficult condition.

3.5.2 Recruitment

Patients attending the Durham Constipation Clinic for chronic constipation and who have already failed to respond to nurse-led interventions (biofeedback or habit training) were eligible for recruitment screening based on the criteria outlined previously.

3.5.3 Visit 0: Pre-Screening: Eligibility assessment

A GCP-trained and delegated local researcher screened potential participants for basic eligibility by phone (or face-to-face interview based on patient choice). Potentially eligible patients were identified in clinic, from referral letters from GPs/other consultants to the constipation clinic. Participants were provided with adequate explanation of the aims, methods, anticipated benefits and risks of anal irrigation therapy and were given an invitation letter and a patient information sheet. Patients were be given at least 24 hours to consider participation and invited to attend clinic for a more detailed discussion with a suitably trained researcher.

The study screening number was allocated as follows:

Study Code 02

Site Code – 3 letter code for each site

Participant Code – 4 digit code given consecutively and attributed at each site

For example the first participant recruited at County Durham and Darlington NHS Foundation Trust was assigned the code 02-CDD-0001.

3.5.4 Visit 1: Screening, consent and baseline assessments

Visit 1 was conducted face to face in clinic by a member of the research team. Clinical examination was performed as per protocol by a clinician within the research team competent to do so. Following a detailed discussion about the trial, potentially eligible patients completed written informed consent, followed by a more thorough screening and confirmation of eligibility for randomisation by brief history and physical examination (the latter if not already performed within the previous 3 months).

For those patients entering the study, additional baseline outcome assessments were conducted. These included several key validated assessments that profile patient characteristics, informing disease pathophysiology and potential predictors of treatment response. All were selected on the basis of trade-off between adequate detail and achievable brevity. These instruments were combined into a single booklet.

<u>Confirmation of Eligibility</u>

<u>Screening/Confirmation of Eligibility</u>

- Standardised history by interview including previous medication usage.
- Clinical examination findings (carried forward if performed previously within last 3 months): standardised exam of perineum/anus/rectum.

Baseline outcome assessments

- Baseline outcome assessments [PAC-QOL, PAC-SYM, EQ-5D-5L & EQVAS, PHQ9, GAD7, CC-BRQ and BIPQ-CC, see endpoints above].
- Baseline 2-week patient diary and journal were given (training and retrospective completion of the patient journal occurred at visit 1 for collection of resource data. Prospective completion occurred until the end of the study, with review at each follow up). Training in completion of the diary was conducted at visit 1 but this was completed at home and returned at visit 2.

Other baseline only assessments

- Constipation (2006) and IBS (2006) modules of Rome III questionnaire.
- Cleveland Clinic constipation questionnaire.
- Brief, chronic pain, autonomic and joint hypermobility assessments.
- St Marks Incontinence score (for concurrent symptoms).

Randomisation performed by a member of the research team

INVEST radio-physiology investigations (See section 3.7.3 below): These were X-ray colonic transit study, anorectal physiology testing, referred to hereafter as 'INVEST'.

There is no defined time period for this, but it was suggested INVEST should be completed within 4 weeks of Visit 1 baseline visit to allow for diary completion before stopping laxatives for INVEST. A maximum of 8 weeks after visit 1 was tolerated to conduct INVEST.

Those with INVEST completed in the previous 12 months did not need these tests repeated and could be booked for visit 2, commencing in a minimum of 2 weeks to allow completion of baseline diary.

3.5.5 Visits 2-3: Interventions

Visit 2:

- Collection of baseline diary completed prior to randomisation and before stopping laxative (i.e. before INVEST in patients who need this done).
- Training in Anal Irrigation - Patients underwent a single nurse-led training session before starting treatment.
- Training in completion of irrigation journal and provision of irrigation journal (completed weekly). The irrigation journal consisted of; volume of water introduced, frequency of use adverse events and side effects e.g. pain, bleeding.
- Start date for home irrigation agreed with the patient (this was to allow for any delay in delivery of equipment). Ideally this should be the same day as Visit 2, or within 1 week maximum. If any issues or delays were encountered, a new commencement date was agreed; This was recorded as a note to file (CRF 8), along with reasons for delay

Visit 2.1

Patients were contacted by telephone by an irrigation nurse 14 days (+/- 3 days) after Visit 2 to ensure no problems have been encountered, including a review of adverse events and concomitant medications.

Visit 2.2 (if needed)

If there were problems expressed by the patient or identified by the clinician, then a further face-to-face training session was offered, including a review of adverse events and concomitant medications. This occurred any time before visit 3 (2 weeks +/- 1 week from visit 2.1) or in conjunction with visit 3 if not before.

Patients continued the self-administered therapy using a commercially-available device until the end of the study. Patients were followed up until the end of the data collection phase of the study (up to 12 months as part of CapaCiTY 02) or until they decided to discontinue either the therapy or the trial follow up. Irrigation was performed at an agreed frequency initially. Once established on this therapy patients could adjust the frequency and volume of irrigation to suit their particular condition.

Information about treatment was recorded in an irrigation journal. This information consisted of: frequency of use of irrigation; volume of water introduced; adverse events and side effects e.g. pain, bleeding. Where a patient switched to the other irrigation device or discontinued treatment (patient choice) the reason for this, as well as the duration of therapy, was documented. If a patient chose to switch devices, which they could do at any stage after the 3 months follow up visit, they received training in the other device. They received follow up by the irrigation nurse as required to resolve any outstanding issues and to check progress. This was documented on the irrigation diary and a note to file completed (CRF 8). However they were not be asked to repeat the questionnaires and diaries.

Visit 3

This took place 2 weeks (+/- 1 week's tolerance if needed) after Visit 2.1. PAC-QOL, PAC-SYM and EQ-5D-5L were recorded at this visit, and irrigation journal was reviewed. A new patient diary, journal and irrigation journal were provided for collection at next follow up visit.

3.5.6 Visits 4-5: Follow-up outcome assessments: visits or telephone consultations

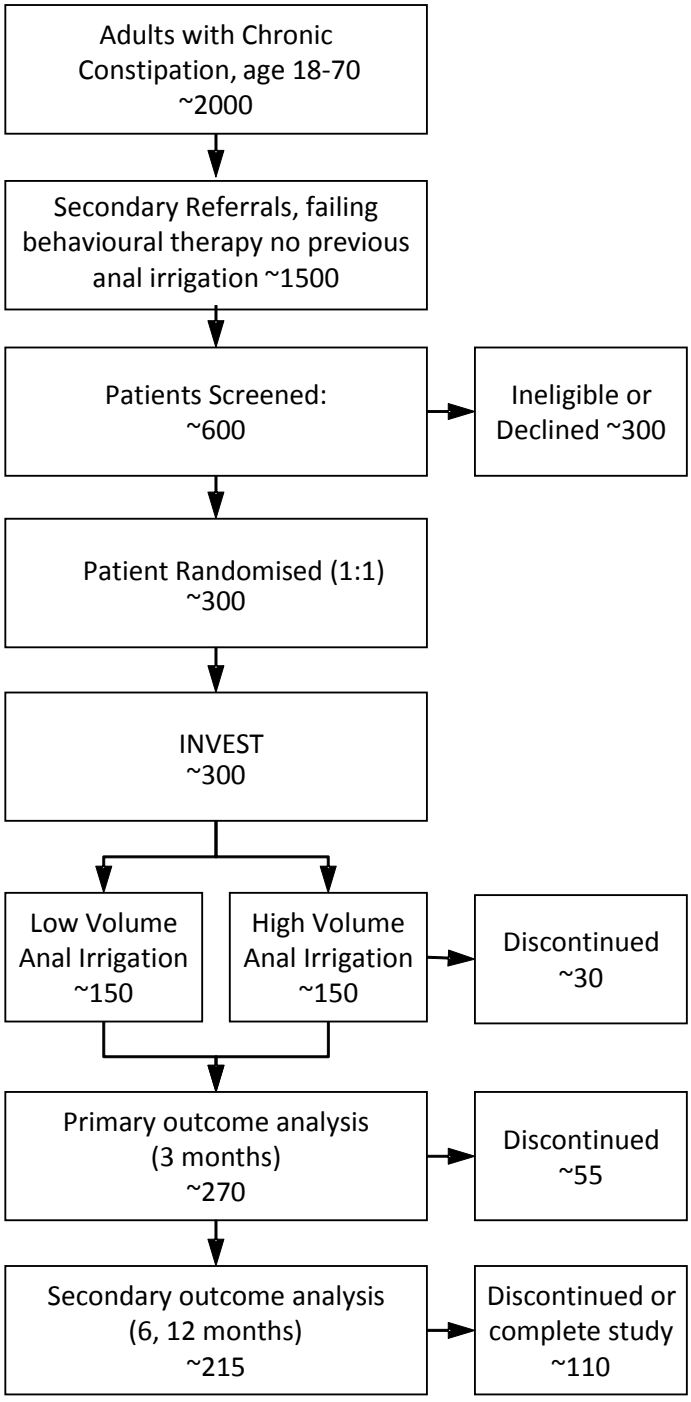
A full standardised outcome framework was recorded at baseline, 3 and 6 months (+/- 1 week) after initiation of intervention at visit 2. To maximise completeness of data collected, follow up visits were conducted face-to-face in clinic wherever possible. Where this was not possible (due to participant or researcher availability), a telephone consultation was used.

For patients remaining on either irrigation method, further full outcomes will be recorded at 12 months as follow-up within the CapaCiTY programme permits. These outcome data are not part of this thesis however.

The patient diary, journal and irrigation journal were provided by the participant for review at each follow up visit to enable CRF completion and accurate reporting of adverse events.

Within the planned study period at least three attempts via two different methods (e.g. phone and letter), were made by research staff to make contact and collect follow up data at each time point, after which the time point was recorded as missing. No patient was regarded as lost-to-follow-up before 12 months unless they asked to withdraw from the study. (See criteria for withdrawal.)

3.5.7 Study Scheme Diagram (CapaCiTY study 02) – Planned screening and estimated recruitment numbers across all sites (n=10)



3.6 STUDY PROCEDURES

3.6.1 Informed Consent Procedures

Written informed consent was obtained at visit 1 from research participants by an appropriately trained member of the research team in a face to face setting in clinic.

3.6.2 Screening, Enrollment

A brief screening questionnaire was used to determine whether patients meet inclusion and exclusion criteria (see eligibility above). Screening was performed by suitably trained study personnel to minimise logistic hurdles, and as determined by geographic availability. In practice, at the Durham site, this was either a research nurse or a doctor.

3.6.3 Randomisation Procedures

Patients were randomised 1:1 into two groups; those who commenced therapy with a low-volume device and those starting with a high-volume device. Patients were stratified by sex and females by centre. Randomisation was performed by a GCP-trained member of the research team using an online system.

3.6.4 Blinding

Patients and clinicians were necessarily aware of both INVEST and treatment allocations. The need to collect data on frequency and volume of irrigation, as well as reasons for discontinuing or switching between systems, meant assessor blinding was not possible with respect to these outcomes. Any researcher collecting CRFs or handling journals was therefore unblinded. However, the primary outcome (PAC-

QOL at three months) was concealed; the patients completed this questionnaire without a researcher present. This was accomplished in one of the following ways;

1. Direct entry to online secure database, with built in validation and prompting to ensure data completeness.

2. Completing paper questionnaire by following instructions on an information card to ensure all questions were answered. This was placed in a sealed envelope marked with the patients pseudonymised study code and was not opened until the time comes for data entry.

3.7 STUDY INTERVENTIONS

3.7.1 Anal Irrigation therapy

Anal irrigation training was provided by trained nurses with experience in delivering care for chronic constipation. They must have initiated irrigation therapy in at least three patients independently, and be a nurse/therapist of good standing within a clinical team regularly seeing patients with chronic constipation. For the first three months of participation in the study, patients could not use other therapies besides anal irrigation and those rescue therapies specified below. They could discontinue therapy at any point (elective withdrawal from intervention) and could choose to switch from one system to the other after 3 months. Switching anal irrigation systems before completing the three-month waiting period was discouraged. If it occurred, it was recorded as a protocol deviation with the timing and reason documented. If symptoms were severe despite use of irrigation and rescue therapies

then other medications could be used on compassionate grounds, but this must be recorded in the CRF/concomitant medications log.

The course of therapy included a nurse-led training session (or more if required to ensure the device was being used effectively) followed by patient-led home irrigation therapy. The low-volume system commonly used in practice is Qufora® Mini (MBH-International). Various high-volume systems are used, all of which have very similar mechanisms of action; these include Peristeen™ (Coloplast) and Qufora-Toilet/Qufora-Balloon™ (MBH-international).

These are commercially-available transanal irrigation systems available on prescription in NHS practice.

Low-volume Irrigation

This system consists of a small reservoir attached to a cone. The reservoir holds approximately 70ml of water and is squeezed to inject water into the rectum. The regime used was as follows: Initial irrigation once daily for 14 days using 1 -3 insufflations (each of 70ml approximately). This could then be reduced to alternate days depending on response. Patients could then adjust frequency and volume depending on response. They could irrigate as much and as often as they felt was necessary to give them benefit and this information was captured on the CRF with the aid of an irrigation journal.

High-volume irrigation

High-volume systems consist of an irrigation bag connected to a tube. The water flows into the rectum, either by gravity or using a pump. Some systems employ a balloon to hold the device in place during irrigation; others require the patient to hold it in place. The mechanism of action is broadly the same for all systems. Initial frequency of irrigation was the same as for low-volume irrigation; i.e. daily for 14 days, then alternate days. Patients commenced with irrigations of 300ml and increased this by 100 ml every two days until satisfactory defecation was achieved or the procedure became uncomfortable, up to a maximum of 1500ml. Patients could adjust therapy depending on response, as for low-volume irrigation.

Training sessions (45-60 min) (V2-V3)

This used a standardised proforma and was always face to face. Feasibility questionnaires were sent to participating sites to establish what their current practice was with respect to initiating irrigation therapy, funding treatment and patient follow-up. Views on the proposed laxative rescue therapy were also obtained. The following training protocol was developed to accommodate these views as much as possible. Patients received:

(a) Regulation/standardisation of laxative use: Bisacodyl could be used orally as a rescue therapy (up to 20mg at night), plus glycerine suppositories 1-2 if needed, if no stool for 3 days. In addition, patients could take Movicol up to a maximum dose of 2 sachets three times per day (TDS) and/or lactulose up to 15ml twice per day (BD). Prokinetic drugs and any other drug that the British National

Formulary (BNF) describes as having laxative effect or herbal teas that contain strong purgatives were discouraged, but if needed (i.e. if symptoms severe) then these were permitted but use must be recorded in the concomitant medications log. There was no use of enemas.

(b) The device was demonstrated to the patient by the nurse specialist and then the patient practiced setting up the device. The trainer ensured the device was being used correctly before home irrigation was commenced. The trainer and patient agreed a date for delivery of equipment and commencement of home irrigation. Ideally this should be the same as the first training visit, but this may not be possible due to delay in supplying irrigation equipment. Any delays were recorded on a note to file (CRF 8) to allow data analysis to be adjusted accordingly.

(c) Plenty of optimism, encouragement and personal attention.

(d) A telephone call was made to the patient 14 days (+/- 3 days) after Visit 2 to check everything was proceeding correctly and to resolve any problems (V2.1). If, due to delay obtaining equipment etc, the patient had not started irrigation at this time then the phone call (and other follow up visits) were re-scheduled for 14 days later, and the reason for this recorded on CRF 8.

(e) If there were problems, a further face-to-face session was offered (V2.2). There was no specific time requirement and this depended on the difficulties encountered and availability of appointments, ideally this visit should have been conducted within a week and before visit 3.

(f) All patients received a further training assessment a 4 weeks (V3). This visit was combined with collection of PAC-QOL, PAC-SYM and EQ-5D-5L, EQ-VAS and

should be face to face. A telephone call was an acceptable alternative if this was not possible.

(g) Patients deciding to switch to the alternative system were trained in the new system by the irrigation nurse, and this was recorded on the note to file, CRF8. These patients did not need to complete the questionnaires at 1 month and 3 months as they had already done so.

(h) Standardised guidance on how to tailor therapy to each patient depending on initial response was provided to specialist nurses. Changes in regimen as well as system were documented on the CRF.

Telephone support was available from the irrigation nurse between visits (number given, office hours only). The therapist completed the intervention CRF at every visit or patient contact. For contact with patients after the training period, a note to file (CRF 8) was completed, and the patient also made a note of any contact in their irrigation journal. In the instance of new psychological issues being determined during consultation, referral for psychological support was deferred until after completion of irrigation training. The exception to this rule was applied if there was clinical concern regarding the patients acute mental state requiring more urgent intervention (see withdrawal from treatment criteria). Further follow-up visits (V4-V8) were conducted by the research team. If the patient required further input from the irrigation nurse this could be arranged as per local practices. Any contact and any changes made or advice given regarding irrigation was recorded in the patient journal and irrigation journal.

3.7.2 Switching between anal irrigation systems

After three months of using one system, patients were allowed to switch to the other or discontinue therapy and return to routine clinical care. This was entirely patient-led, and reasons for changing systems were explored during follow up visits and captured on the CRF. There was therefore no defined protocol for switching treatments as patients could do this for any reason; analysis of time to switching/discontinuing therapy, as well as the patient-reported reasons for doing so, provided insight into why each irrigation system was or was not successful. In addition, qualitative interviews with patients who switched or discontinued therapy were used to explore these issues more deeply (see chapter 4 'Qualitative Methodology')

3.7.3 INVEST

Radio-physiological investigations

Patients underwent standardised investigations. If INVEST had previously conducted within the last 12 months, results could be carried forward. Pregnancy testing was conducted as per routine NHS practice (10 day NHS rule) in respect to women between menarche and menopause. Women of equivocal status had a serum pregnancy test performed as per routine care.

(a) Anorectal manometry using standard or high resolution methods(83–85) to determine defined abnormalities of rectoanal pressure gradient during simulated evacuation(86,87).

(b) Balloon sensory testing using standardised methods (2ml air per second to maximum 360 ml) to determine volume inflated to first constant sensation, defecatory desire and maximum tolerated volumes. The rectoanal inhibitory reflex was also elicited by 50ml rapid inflation (if necessary in 50 mL aliquots up to 150ml).

(c) Fixed volume (50ml) water-filled rectal balloon expulsion test(86,88) in the seated position on a commode. Abnormal expulsion was defined as abnormal if failure to expel with 1-minute effort for men and 1.5 minutes for women(89).

(d) Whole gut transit study using serial (different shaped) radio-opaque markers over 3 days with single plain radiograph at 120 hours(90).

Treatment

All patients underwent trans-anal irrigation therapy irrespective of INVEST results, and were followed up in the same way. The purpose of INVEST in this study is to identify whether certain radio-physiological results correlate with treatment response, i.e. can we predict likelihood of benefitting from irrigation based on pre-treatment investigations.

3.7.4 Concomitant Medications

It was inevitable that patients would seek recourse to laxatives and other dietary supplements during the course of the programme. Experience shows that complete prohibition can lead to unreported laxative use, which might confound findings. Although we strongly discouraged *ad libitum* medication usage and specified a defined breakthrough regimen, we aimed to record co-treatment with sufficient fidelity and integrity to enable use these as covariates in analyses using a specific patient journal for this purpose. A concomitant medications list including a shortlist

of contributory or confounding medications was used to filter on data entry. Patients using one system in the medium/long term could revert to the other system or pause treatment for a short period (for example while going on holiday) for practical reasons. This was permitted but must be recorded in the concomitant medications log. This short-term break in treatment was not considered as switching or ending treatments.

3.7.5 Criteria for Discontinuation

The interventions proposed are well-established in current clinical practice. There were no defined criteria for discontinuation; however clinicians could withdraw treatment where they had therapeutic or safety concerns, consistent with routine care. Patients could choose to discontinue treatment at any point and return to routine clinical care. Participants had the option of continuing to attend for follow up visits or to discontinue trial participation entirely. Any data collected up to this point were included in the analysis unless consent was withdrawn.

3.8 FOLLOW-UP PROCEDURES

The CapaCiTY 02 study duration allows for follow up to a maximum of 12 months with data collection at 3, 6 and 12 months post commencement of therapy. Primary outcome data were collected at three months. In addition, PAC-SYM, PAC-QOL and EQ-5D-5L, EQVAS were recorded at the 1-month visit; this was to capture information on early non-responders, and to better understand and characterize this group of patients.

Thereafter, participating patients could leave the study and return to 'routine clinical care' as determined within their local NHS institution (or be recruited to subsequent trials). Alternatively they may wish to proceed to enrolment in the next work package (Study 3 – Laparascopic Ventral Mesh Rectopexy) within the CapaCiTY programme. For the purposes of this thesis, data collected up to 6 months from University Hospital of North Durham were analysed.

3.8.1 The following data were collected at each visit up to 12 months:

- Validated symptom and quality of life questionnaires (PAC-SYM and PAC-QOL).
- A two week patient diary (for 2 weeks before each assessment) to record bowel frequency and whether each evacuation was spontaneous (no use of laxatives) and/or complete; a patient journal also captured concurrent medication, health contacts, time away from normal activities (including work). Patients were contacted by telephone to remind them to start the diary. If patients forgot to do this, then it was acceptable for them to start recording the diary on the day they are seen in clinic and for this to be collected two weeks later.
- Irrigation journal to record frequency and volume of irrigation and any adverse events.
- Validated generic QOL questionnaires: EQ-5D-5L descriptive system and EQ-VAS. Note: EQ-VAS has a SD of approximately 30 points: a 10% difference in VAS deemed clinically significant can be detected with the large sample sizes proposed.

- Resource use data (using patient journals as a prompt and including concomitant medication use).
- Patient Health Questionnaire-9 (PHQ-9).
- Generalized anxiety disorder questionnaire (GAD7)
- Depression, anxiety and somatisation modules of the Patient Health Questionnaire. Brief illness perception questionnaire.
- Global patient satisfaction/improvement score (VAS) and whether they would recommend each treatment experienced to other patients.
- Potentially modifiable cognitive and behavioural psychological variables shown to predict onset and perpetuation of other functional bowel symptoms: negative perfectionism, avoidant and 'all or nothing' behaviour subscales of the behavioural response to illness questionnaire (CC-BRQ), and brief illness perception questionnaire BIPQ (CC).

3.8.2 Laboratory Assessments

Serum Pregnancy Testing was performed as per standard care for any women of equivocal status undergoing radiological assessments (INVEST).

3.8.3 Radiology Assessments

The whole gut transit study usually (90% patients) involved the use of a single plain abdominal radiograph (in 10% patients, a maximum of 2 may have been required to image whole abdomen and pelvis). This test forms part of routine clinical care for patients with CC at many NHS centres. All practitioners (radiologists, radiographers etc.) directing these studies held appropriate IR(ME)R certification.

3.8.4 Participant withdrawal (including data collection / retention for withdrawn participants)

Individual participants were able to withdraw from treatment at any time by notifying healthcare professionals involved with the study, and return to routine care without prejudice. Data will be retained for intent to treat analysis from all participants after the point of consent and recruitment, unless participants withdraw consent for this.

Withdrawal from treatment Criteria:

Participant developed any of the following exclusion criteria

- Participant became pregnant or intended to become pregnant (only in baseline and intervention phases).
- Participant subsequently diagnosed with proven cause for secondary constipation e.g. Parkinson's disease or bowel obstruction.
- Participant required new medication with proven effects on bowel function e.g. opioids.
- Participant developed significant intercurrent illness precluding participation.
- Participant required surgery or other intervention (other than minor ops) during treatment or follow up phase.
- Patient developed acute psychological problem causing safety concern.
- Adverse events secondary to therapy (bleeding, anal fissure, ulceration, pain, bowel perforation) – relative indications for withdrawal depended on the views of the patient and doctor (NB perforation was an absolute indication for withdrawal).

- Elective withdrawal.

Loss to Follow Up (no further interventions or follow up data collected)

- Participants could be withdrawn from the trial if they become lost to follow up (LTF) after at least 3 failed attempts by research staff to make contact via 2 different methods (e.g. phone and letter).
- Participant chose to withdraw and did not wish to participate in follow up data collection.
- Death or significant incapacity making follow up data collection impossible.

3.8.5 End of Study Definition

The end of study is defined as the last patient last visit. The sponsor, REC and local R&D departments will be informed of end of study and site closure and archiving procedures initiated. For this thesis, patients recruited at University Hospital of North Durham with a minimum of three months' outcome data by 1st October 2016 were eligible to be included.

3.8.6 Criteria for Early Termination

If the Data Monitoring Ethics Committee (DMEC), Programme Steering Committee (PSC), Research Ethics Committee (REC) or sponsor determined it was within the best interests of the participants or trial to terminate the study, written notification would have been given to the CI. This may have been due to, but not limited to; serious safety concerns, serious breaches, acts of fraud, critical findings or persistent non-compliance that negatively affects patient safety or data integrity. If the study was terminated participants would have been returned to the NHS normal follow up and routine care. This did not occur during the trial period presented here.

3.9 STATISTICAL CONSIDERATIONS

3.9.1 Sample Size calculation for CapaCiTY 02

PAC-QOL is a 28-item disease-specific measure, with each item scored 0-4, and providing an aggregate score 0-4(76). Following discussions between the trial statistician, the chief investigator and clinical lead, it was deemed appropriate to assume that a clinically important difference in superiority comparing low volume with high volume anal irrigation would be demonstrated by a 10% scale difference (or more), or 0.4, with a variance estimate conservatively set at SD=1 from the published literature(91) To detect an effect size of 0.4 (mean/SD =0.4) between the two groups with 90% power and 5% significance at three months requires 133 patients per arm, and 266 total. Allowing for an anticipated 10% loss to follow up (LTFU), then a total sample size of 300 participants was decided upon. With approximately ten sites recruiting, this equates to a proposed recruitment rate of approximately 1 participant per month per site for the two-year recruitment period. The data presented here are for one site for the first year of recruitment, with the aim of conducting a feasibility analysis.

3.9.2 Method of Analysis

Clinical Outcomes

Given the proposed recruitment target rate of one participant per month per site, the sample size for this MD study was very much smaller than for the CapaCiTY 02 study as a whole. Therefore meaningful analysis is limited to a descriptive analysis of the study findings and a discussion of their implications for the wider study, with particular focus on accuracy and completeness of data collection, adherence to the

follow up plan and rate of recruitment. Additionally, the standard deviation of the primary outcome measure (PAC-QOL measured three months after starting treatment) was calculated to further evaluate the appropriateness of the sample size calculation. Final analysis was by intention-to-treat. Statistical calculations were performed using Stata 12 (StataCorp, Texas, USA). A full statistical analysis plan for the CapaCiTY 02 study has been developed; the key components of this are outlined below.

CapaCiTY 02 study analysis plan

All analyses will be by the intention-to-treat principle. The primary outcome will be PAC-QOL as a continuous variable, analysed at 3-months. The proportion of patients continuing with the initial therapy system will be recorded, and the PAC-QOL scores will be analysed using a linear mixed model with a random effect for centre and fixed effects for intervention, trial stratification variables (participants are stratified by sex and females by centre) and baseline PAC-QOL. Secondary outcomes will be analysed using the principles outlined for the primary outcome.

Exploratory modelling will be conducted for baseline characteristics: measures of chronic pain, autonomic, joint hypermobility, cognitive, behavioural and mood variables share a common hypothesis that they are detrimental to the success of all treatments i.e. they perpetuate illness in spite of therapy. We will investigate a maximum of 3 interactions between treatment and baseline characteristics.

Life table data for any irrigation will be presented by initial therapy and for specific therapy from date of commencement. Survival analysis will be presented using

Kaplan Maier analysis and adjusted using Cox regression. Exploratory analysis will be considered to identify characteristics of sub-groups with greatest persistent benefit from irrigation.

Health economics analysis will also be performed using data transferred to the CRF from the patient journal. This will include comparative analysis of cost per success and cost per QALY, in order to explore overall cost effectiveness of treatment. This will be combined with health economics outcomes from the other work packages in the CapaCiTY programme in order to model optimal treatment pathways from a cost effectiveness perspective.

3.10 ETHICS

3.10.1 General

This study (Study 2 of the CapaCiTY programme) is being carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

Ethics approval for the CapaCiTY 02 study was granted by the London City and East Research Ethics Committee (REC) (study reference number 15/LO/0732). Major protocol amendments were also approved by the same body. The study was registered with ISRCTN (registration number ISRCTN44563324) in accordance with national governance requirements.

3.10.2 Ethical considerations

The CapaCiTY 02 protocol was independently peer reviewed by Prof Richard Ashcroft, Professor of Medical Ethics and Law at Queen Mary University of London (QMUL). Important considerations that informed pragmatic design include (a) *limitation of intimate examinations:* to one time point (not repeated if performed before recruitment); (b) *timings of outcomes*: Within this study outcomes were measured at 3 and 6 months from the commencement of the first treatment for all patients, with additional recording of key outcome measures (PAC-QOL, PAC-SYM, EQ-5D-5L, EQ-VAS, Irrigation Journal and Patient journal). For this period of 6 months, patients did not progress to further Work Packages (the term used within the CapaCiTY programme to describe each stage of the research programme), thus preventing outcome 'contamination'. Additionally there was a 3 month 'quarantine' from switching irrigation therapy. These delays were akin to that in usual NHS care, during which general supportive care was provided. These proposed limitations at 3 and 6 months conferred no disadvantage and may even have represented an acceleration of treatment progression. Ethically, this was viewed as a reasonable trade-off for the commitment to the research programme; (c) *recruitment & consent*: study 2 represents one of the 3 studies incorporated in the NIHR-funded CapaCiTY programme. Although patients may have moved sequentially through treatments (and therefore studies) during the programme course, study 2 was consented as a distinct single entity;

3.10.3 Competing interests

The investigating team declared no conflicts of interest.

3.11 SAFETY CONSIDERATIONS

Patients recruited who had not had previous INVEST procedures conducted within the last 12 months underwent one radiological procedure (whole gut transit study) using ionising radiation as outlined above. The combined dose of this procedure (~0.1mSv) was equivalent to approximately 2.5 weeks annual background radiation dose from living in the UK [NB: this is an approximation which will require re-certification by Barts Health NHS Clinical Physics Dept. based on doses from 20 equivalent procedures]. Furthermore, this investigation would be carried out in routine clinical practice in many centres for patients at the same point as recruitment to this study.

Regarding the intervention, anal irrigation is associated with a very small incidence of bowel perforation, as well as other side effects (bleeding, pain, ulceration, painful haemorrhoids, anal fissure) (58). These have been outlined in more detail in Chapter 2. Patients were counselled and fully informed verbally and in writing within the ethically approved patient information sheet regarding these risks as part of the process of informed consent. In addition, they were trained in the correct use of the device before commencing therapy. All adverse events and serious adverse events were recorded and therapy suspended while these are investigated

3.12 DATA HANDLING AND RECORD KEEPING

3.12.1 Confidentiality

Information related to participants was kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research

Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

Identifiable information collected from the participants included; full name, DOB and hospital number and contact details at screening. This information was used to contact participants but did not leave the study site without prior consent and approvals. All case report forms were pseudonymised. The participant's GP was informed of their participation in the quantitative study.

The trial data were made available to suitably qualified members of the research team, study monitors and auditors, the sponsor, the REC and regulatory authorities as far as required by law. The participants will not be identifiable with regards to any future publications relating to this study.

3.12.2 Record Retention and Archiving

When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records (including paper records, digital records and audio files) are kept for a further 20 years. For trials involving Barts and the London NHS Trust patients, undertaken by Trust staff, or sponsored by Barts and the London or Queen Mary University of London, the approved repository for long-term storage of local records is the Local Trust Modern Records Centre.

3.13 SAFETY REPORTING

3.13.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

Notification and reporting Adverse Events or Reactions

The anal irrigation systems are in widespread and established clinical use throughout the NHS with known adverse events occurring (22%) being mostly minor and reversible. All trial interventions were as per the standard care provided within the NHS for chronic constipation. Adverse events were recorded on the CRF. Serious adverse events were recorded on the CRF and in the medical notes to enable assessment and reporting in line with sponsor and regulatory requirements. Causality was at the discretion of the health care provider (e.g. research nurse, physiotherapist, principal investigator or delegated member of team). These were assessed as outlined below.

Trial participants were advised to seek medical support from their GP for any unrelated signs, symptoms or disease or aggravation of underlying symptoms.

3.13.2 Serious Adverse Event (SAE)

In other research other than clinical trials of investigational medicinal products (CTIMPs), a serious adverse event (SAE) is defined as an untoward occurrence that:

(a) Results in death.

(b) Is life-threatening.

(c) Requires hospitalisation or prolongation of existing hospitalisation.

(d) Results in persistent or significant disability or incapacity.

(e) Consists of a congenital anomaly or birth defect; or

(f) Is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant was reported to the main REC where in the opinion of the Chief Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

3.13.3 Notification and Reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that were considered to be 'related' and 'unexpected' were reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe.

3.13.4 Expected SAEs

The following SAEs were expected to occur rarely in this patient population and were not reported:

- Hospital admission for exacerbation of constipation symptoms including impaction.
- Hospital admission for unrelated elective surgical procedures or accidental injury.

3.13.5 Urgent Safety Measures

The CI was responsible for taking urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures would have been taken immediately. In this instance, the approval of the REC prior to implementing these safety measures was not required. However, it was the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI had an obligation to inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) would be sent a copy of the correspondence with regards to this matter. However, no such issues were encountered during the study period considered in this thesis.

3.14 PATIENT-PUBLIC INVOLVEMENT AND SITE FEASIBILITY QUESTIONNAIRE

3.14.1 Patient-Public Involvement (PPI)

Prior to study commencement, a selection of chronic constipation patients were asked to complete a short feasibility questionnaire regarding the study methodology. These patients were attending the Durham Constipation Clinic, and participation was entirely voluntary. They were not asked to commit to enrolling in the study, nor were they screened for suitability for inclusion.

The following questions were asked:

- Do you mind random allocation of system?
- Would you be happy to wait 3 months before switching systems?
- Are you happy with restricted laxative use?
- Would you participate in this study if you were eligible?

Patients were also asked if they would consider reviewing the full research protocol.

Additionally, some study documents (Patient Information Sheet, Journals and Diary) were given to patients for review and comment.

Members of the local Constipation Research Advisory Group (CRAG), consisting of patients not directly involved with the study, were also asked to complete the baseline questionnaire booklet, and to provide feedback on this. This was completed during a group seminar. Clinicians and research team members also completed the questionnaires. Participants were asked to record the time taken to complete each questionnaire, and also to score each questionnaire for relevance and ease of use, using a five-point Likert scale from 1 (very relevant/ very easy) to 5 (not at all relevant/ very difficult). The results of this feasibility exercise are reported in Chapter 5 (page 103).

3.14.2 Site Feasibility

As a multi-centre trial, it was important that the methodology used was acceptable and applicable across several hospitals. Therefore, a site feasibility questionnaire was sent to all prospective participating centres. The questionnaire was sent to thirteen sites, and responses were received from nine. Questions centred on the

following areas: how patients are trained to use irrigation and how the proposed methodology compared to this; how patients are followed up (both frequency and method of follow-up); which irrigation systems are used, and who prescribes these; reasons given for switching or discontinuing therapy in clinical practice; views on the suitability of the proposed rescue therapy; availability of resources to allow allocation of one blinded and one un-blinded researcher. See Chapter 5 (page 101) for a summary of the findings of this questionnaire.

3.15 CONCLUSIONS

This study methodology was designed to provide a balance between rigorous randomised assessment of an intervention and a pragmatic approach that takes into consideration the reality of the clinical situation encountered. This resulted in the unusual element of allowing patients to switch between irrigation systems after the 3-month primary endpoint measurement. This design allows reasonable comparison of the two systems under experimental conditions for a long enough time period for superiority of one system to be established, but also limits the time patients spend using this treatment if it is ineffective for them.

Equally, the decision to allow controlled laxative use acknowledges the clinical reality that many patients require laxative medications alongside irrigation therapy in order to manage their symptoms effectively.

Further design issues concern the impracticality of assessor blinding, given that data collection inevitably leads to the assessor becoming un-blinded. In order to reduce

the impact of bias, the decision was made to conceal the primary outcome (PAC-QOL) questionnaire as detailed earlier in the chapter.

Also, the placebo effect of this treatment may be significant; it was not possible to devise a suitable placebo for irrigation, therefore several options were explored. A cohort study without randomisation was not deemed sufficiently robust, and a waiting-list controlled trial would be equally vulnerable to the placebo effect and would not provide a comparison between systems. Therefore the present design was adopted, with the view that the placebo effect should be similar for both systems therefore any difference between the two would be a genuine difference related to the comparative effectiveness of each system.

CHAPTER 4: QUALITATIVE STUDY METHODOLOGY

4.1 INTRODUCTION

Patients with chronic constipation have reported dissatisfaction both with the effects of their illness on their quality of life and with some health professionals' attitudes towards them and their condition (36). There is evidence that some clinicians hold pejorative opinions about patients with functional gastrointestinal disorders(92) and that this is noted by the patients, leading to frustration and discontent from either or both parties (36)(92). The view that the condition is 'all in the mind' can lead to patients being labelled negatively, and patients' feelings of dissatisfaction at not being taken seriously are well described; many feel that a functional diagnosis means their symptoms are not being granted legitimacy in the eyes of the medical profession (36). Although psychosocial factors contribute to symptoms in many cases and should be addressed(38), a perceived 'dismissing' of symptoms as entirely psychological can have a negative impact on the therapeutic relationship (36).

4.2 BACKGROUND AND RATIONALE

Trans-anal irrigation therapy (TAI) is in widespread use throughout the UK as a treatment for bowel dysfunction. It has been used successfully to treat adults and children with neurogenic constipation (46)(47)(48), and faecal incontinence(49). However, the case for trans-anal irrigation therapy for chronic functional

constipation in adults is not universally accepted, and there are questions about long-term benefit (58).

Despite the significant burden of disease associated with chronic constipation and the invasive nature of trans-anal irrigation therapy, there is relatively little evidence to support its use or to explore the patient experience of training or using in their everyday lives. A systematic literature review was carried out using the terms: bowel dysfunction, defecation, constipation and irrigation; the databases Embase, Medline, Evidence-Based Medicine (EBM) reviews and Cumulative Index to Nursing and Allied Health Literature (CINAHL) yielded a total of seven original quantitative research articles studying anal irrigation (See Chapter 2). These were all prospective or retrospective uncontrolled studies; a meta-analysis suggested that approximately 50% of patients experienced an improvement in their symptoms using trans-anal irrigation. One piece of qualitative research, conducted by Tod et al (2007)(93), explored patients' experiences using rectal irrigation and found that these were generally positive, with significant improvements in quality of life experienced by most patients. Key themes included regaining control over their symptoms, increased confidence, improved social participation, improved personal relationships, and the importance of the care delivered by clinical staff. However, this study only recruited women from a diagnostically undifferentiated group and did not explore the process of irrigation training or fidelity to treatment. Additionally, this was the only qualitative study found in the literature that sought to explore specifically the experiences of patients undergoing trans-anal irrigation. Therefore, the present study will add to the limited body of qualitative research in

this area by exploring patients' lived experiences of using irrigation, as well as reasons for the success of failure of therapy from the point of treatment commencement onwards.

4.3 AIMS

The purpose of this qualitative enquiry is to complement an ongoing clinical trial of trans-anal irrigation by exploring the patients' lived experience of learning, using, and continuing irrigation. A phenomenological methodology was employed and qualitative data were collected in parallel with the trial.

4.4 RESEARCH QUESTION

4.4.1 Primary research question

- What is the essence of the patient's lived experience of using trans-anal irrigation therapy for the treatment of chronic constipation?

4.4.2 Secondary research questions

- How was the process of training to use irrigation, experienced by patients?
- How was the process of follow-up support in the use of irrigation, experienced by patients?
- What factors did patients take into account when deciding whether to continue with therapy, and how was this acted upon?
- How did the patient experience differ between patients who continued or discontinued therapy?

- Were there differences in the patient's experience of high-volume and low-volume irrigation?

4.5 THEORETICAL FRAMEWORK

This study employed a phenomenological framework. This approach seeks to define the 'essence' of the experience of a particular phenomenon (in this case, undergoing trans-anal irrigation therapy for chronic constipation) from the point of view of the person going through it. It has a strong philosophical basis, the core idea being that phenomena are perceived by humans as 'lived experiences', and that, by bringing together themes that emerge through conducting interviews with people who all share experience of a particular phenomenon, the researcher can weave together a description of the essence of the experience(94) . It is important for the researcher to set aside any presuppositions regarding the phenomenon and to suspend judgements regarding 'truth' until a foundation for these beliefs has been established(94). The phenomenon exists within the meaning of the participants' experience rather than being seen as having an objective reality independent of consciousness (94).

This approach has been used in healthcare research to explore a wide range of topics, for example fatigue in chronic illness(95), HIV/AIDS (96) and heart failure(97). It enables the researcher to understand how a particular experience is perceived by those going through it. In this case, this was conducted within a clinical trial that

aimed to assess the effectiveness of the treatment. The combination of qualitative and quantitative methods enables a very rich description of the treatment.

A phenomenological approach was chosen in preference to other qualitative methods (for example, grounded theory) as comparatively little is known about the patient's lived experiences of using irrigation. It is not known whether different themes will emerge depending on which system was used initially, or whether patients discontinue or switch treatment. A grounded theory study (for example, to establish a theory of why patients discontinue anal irrigation) would be a valuable exercise but is narrower in scope, risks imposing a researcher-biased framework, and may well require a larger number of participants. A phenomenological study, therefore, enabled many aspects of the experience to be described and provided valuable insights into what irrigation treatment is like. This can, in turn, enable health professionals to counsel people undergoing this therapy as to what to expect, and to better understand patient perspectives about treatment.

There are some disadvantages to this approach. Small numbers of patients may limit generalisation of findings beyond the group of patients studied. Also, there is a need for the interviewer to be neutral, and to divest themselves of any pre-conceived ideas regarding the phenomenon. This could be difficult to achieve, especially for a clinician interviewer. These challenges were addressed via regular supervision with

an experienced qualitative researcher (HC). The potential challenges of this aspect of the study are explored further in section 4.12 of this chapter.

Within the framework of phenomenology there are two approaches; 'hermeneutic' phenomenology and 'transcendental' phenomenology. Broadly speaking, hermeneutic phenomenology aims not only to describe the lived experiences of the phenomenon being studied, but also to interpret the meaning of these experiences. Transcendental phenomenology, by contrast, is focussed on describing the essence of the experience. This requires the researcher to 'bracket' their experiences of the phenomenon in order, as far as possible, to try to perceive it as if for the first time. As the aim of this qualitative study was to define the essence of the experience rather than place emphasis on the researcher's interpretation of this, a transcendental approach was taken. However, it is acknowledged that it was not possible to eliminate a degree of interpretation in the analysis.

4.6 RESEARCH STRATEGY

4.6.1 Inclusion Criteria

- Age 18-70 years
- Patient self-reported problematic constipation
- Symptom onset > 6 months before recruitment
- Symptoms met American College of Gastroenterology definition of constipation

- Constipation failed treatment to a minimum basic standard (lifestyle AND dietary measures AND≥2 laxatives or prokinetics) tried (no time requirement)
- Ability to understand written and spoken English (due to interview validity)
- Ability and willingness to give informed consent
- Failure of previous nurse-led behavioural therapy
- Ability of patient / carer to use anal irrigation
- Consent to enrollment in the CapaCITY trial

The study used the American College of Gastroenterology definition of constipation;

'Unsatisfactory defaecation characterized by infrequent stool, difficult stool passage or both for at least previous 3 months' (2).

4.6.2 Exclusion Criteria

The study interventions necessitated the exclusion of major causes of secondary constipation in detail:

- Significant organic colonic disease (red flag symptoms e.g. rectal bleeding if not previously investigated); IBD; megacolon or megarectum (if diagnosed beforehand); severe diverticulosis/stricture/birth defects deemed to contribute to symptoms (incidental diverticulosis not an exclusion)
- Major colorectal resectional surgery
- Current overt pelvic organ prolapse (bladder, uterus, vagina, rectum) or disease requiring surgical intervention

- Previous pelvic floor surgery to address defaecatory problems: posterior vaginal repair, STARR and rectopexy; previous sacral nerve stimulation
- Previous use of transanal irrigation therapy to treat constipation
- Rectal impaction (as defined by digital and abdominal examination)
- Significant neurological disease deemed to be causative of constipation e.g. Parkinson's, spinal injury, multiple sclerosis, diabetic neuropathy (not uncomplicated diabetes alone)
- Significant connective tissue disease: scleroderma, systemic sclerosis and SLE (not hypermobility alone)
- Significant medical comorbidities and activity of daily living impairment [based on Bartell index in apparently frail patients,[Bartel index <=11]
- Physical disability/impairment which prevented use of one or other of the irrigation devices
- Major psychiatric diagnosis [schizophrenia, major depressive illness, mania, self-harm, drug/alcohol addiction]
- Chronic regular opioid use (at least once daily use) where this was deemed to be the cause of constipation based on temporal association of symptoms with onset of therapy; all regular strong opioid use.
- Pregnancy or intention to become pregnant during study period.
- Inability or unwillingness to attend interviews.

4.6.3 Sampling strategy

A purposive sample of approximately 4-12 patients were invited to interview upon completion of irrigation training. The plan was then for a further 8-16 patients were interviewed at 6 months (these may be the same or different patients). Recruitment could be extended if data saturation was not accomplished by the 12th patient. Data saturation was defined as the point at which no new or relevant themes emerge. Inclusion and exclusion criteria were as above.

A review of a database of approximately 1,000 adult patients attending a chronic constipation clinic revealed a male:female ratio of 1:9, with a median age of 41 (18-70). It can be reasonably assumed that this reflects the typical demographic make-up of patients with this condition in this region. Therefore sampling was stratified to reflect this as far as possible, with recruitment of approximately equal numbers of patients aged <40 years and >40 years. Male patients were not excluded even though they are uncommon in the study population. Stratification by ethnicity was unlikely to be meaningful, as 94.9% of the population of North East England is 'white British' or 'white other' (98), and there was no evidence to suggest that the demographic of the study population would differ from this.

An approximately equal number of patients were selected from each trial arm as follows:

- 2-6 patients undergoing low-volume anal irrigation and 2-6 patients undergoing high-volume irrigation were selected for interview at one month (+/- 2 weeks)
- Further interviews were planned six months after starting treatment with 8-16 patients including;
    - those who discontinue early (<3 months),
    - later (3-5 months),
    - those who continue with their allocated treatment to at least 6 months,
    - those who switch systems.

Patients enrolled in the quantitative arm of the CapaCiTY 02 study were stored on a research database. Purposive sampling was used to select patients based on age and irrigation system (baseline interviews – 1 month), and duration of therapy (6-month interviews) as outlined above.

4.6.4 Sampling grids

At 1 month (+/- 2 weeks)

	High-Volume	Low-Volume
Age =<40	1-3	1-3
Age>40	1-3	1-3

At 6 Months

	Active user at 6 months	Early discontinuation (<3 months)	Late Discontinuation (3-5 months)	Switch systems
Age =<40	1-2	1-2	1-2	1-2
Age >40	1-2	1-2	1-2	1-2

It should be noted that these proposed sampling grids reflect the 'ideal' situation, and that numbers recruited were limited by delayed recruitment to the study overall. This, and its potential for introducing sampling bias, is detailed further in Chapter 6.

4.7 PROCESS AND PROCEDURE OF RECRUITMENT AND DATA COLLECTION

All patients were told that they may be invited for interview when they were initially informed about the study. A purposive sample of patients as described above was contacted by telephone by CE with support from the clinical team and if willing to be interviewed they were given a patient information sheet. This was then followed up with a phone call after a minimum of 24 hours to establish verbal consent and set up a mutually convenient interview time and date. Participants were offered a semi-structured interview in a clinic room immediately before or after their 4-week or 6-month clinic visits (as appropriate); if the patient was unable or unwilling to be interviewed in this setting then a separate appointment was arranged. They could

request a chaperone to be present if they preferred. Following written consent, the interviews were recorded on a digital dictaphone and transcribed into a pseudonymised (alphanumeric code) text document. Interviews were planned to be conducted by a Clinical Research Fellow at UHND (Christopher Emmett) and/or a Health Research Methodologist at Durham University (Dr Helen Close). Following in-depth training which took into consideration bracketing and the ways in which CE might step into a non-clinical research role, it was decided that all interviews would be held by CE with close supervision from HC. Both CE and HC reviewed the audio file and its transcription file shortly afterwards to ensure appropriate academic supervision, and to assess data saturation.

Interviews explored patients' experiences of recruitment, individual interventions, their training and delivery, and patients' views about outcome measures. Interviews at both time points (1 and 6 months) were semi-structured in nature and allowed the participants considerable freedom to discuss the issues that were most important to them. Questions were necessarily very general, with the aim of eliciting the broadest possible range of responses from patients in order to ensure all major themes were recorded. Overly prescriptive/detailed interview schedules would risk leading patients to address particular issues of importance to the researcher without exploring the full range of patient experiences and therefore resulting in a biased or incomplete description of the patient experience. Interviews lasted between 10 and 20 minutes on average, although the upper time limit set beforehand was 60 minutes.

4.8 TRANSCRIPTION

Interviews were recorded onto a digital recorder. The planned process for data transfer was for these audio files to be uploaded as encrypted files to a secure Durham University data transfer service. This would allow secure transfer of the files. Funding for transcription of qualitative interviews within the CapaCiTY programme was allocated to Kings College London; the files would be transferred securely to Kings College for transcription and then the pseudonymised transcripts would be returned to Durham in a secure fashion (encrypted electronic transfer/recorded delivery) to allow analysis as part of this thesis. However, due to unforeseen problems with the data transfer service and due to software compatibility problems between the trusts, all interviews were transcribed at Durham by CE in order that they could be reviewed and analysed in a timely way. The advantages and disadvantages of this approach are discussed in Chapter 6 (page 125).

4.9 TIMING

Patients were invited to one-to-one interviews on completion of irrigation training. Patients were recalled up to 6 months after training and offered an interview. For the 1-month interviews, these were required to take place no later than 4 weeks after their 1-month visit to maximise recall. There was no specific time limit for the long term interviews, but they must have taken place no earlier than the day of the participant's six-month visit. The patients interviewed at baseline did not have to be

the same as those interviewed up to six months in order to capture the range of types and continuation of treatment. Interviews were timed to capture relatively early and later experiences and perceptions of the interventions.

4.10 ANALYSIS

Interviews were digitally recorded, anonymised, transcribed verbatim and analysed using a pragmatic thematic analysis for data management. Data analysis was developed as outlined by Fereday & Muir-Cochrane(99), following a phenomenological framework; in the first instance by mapping key concepts derived from the transcripts ('charting') and extracting emergent themes from the transcripts. Textural description and structural description of these themes was developed and synthesised into a composite description of the phenomenon, incorporating 'what' the patients experienced and 'how' they experienced it (94). Independent analysis was conducted by CE and HC. Emergent themes, together with captured observational data, will form the basis of joint analytical interpretation with the wider study team including CN (for the larger CapaCiTY 02 study). This wider analysis does not form part of this thesis.

4.11 ETHICAL APPROVALS

The study protocol, comprising both quantitative and qualitative elements, was approved by the NHS REC (London – City & East) (study reference number 15/LO/0732)

4.12 RISKS AND HAZARDS

Interviews were in-depth and conducted one-on-one (or with a chaperone if requested by the patient) and therefore there were potential (minimal) risks to the safety of the interviewer. The intensely personal and private nature of the interviews could have led to psychological distress for the participant. It was therefore necessary to identify patients who would be at especially high risk in either of these ways and to exclude them from the study. Baseline assessment would identify and enable exclusion of individuals with pre-existing psychiatric disorders or a history of high-risk behaviours (self-harm, drug and alcohol addiction). A process of full informed consent took place for each patient as part of the clinical trial before any involvement in the qualitative study took place (which has a separate consent form). HC and CE are both experienced clinicians used to dealing with patients in distress. HC is an experienced qualitative researcher who offered appropriate supervision to CE following each interview.

4.13 RESEARCH RELATIONSHIPS

Because a practising clinician (CE) conducted qualitative interviews, there were potential challenges regarding maintaining a degree of objectivity and allowing patients to express themselves freely. The patient must be allowed to take control of the interview and to dictate the direction of the conversation. This involved a conscious setting aside of the 'clinician persona' and it was emphasised to the participants that the interviewer was a neutral figure interested in them and their

experiences, and not attempting to resolve/address any clinical issues that arise. This was emphasised at the start of the interview, and again if any attempt was made by the participant to ask a clinical question. In this instance, they would have been asked to note down the question and contact the clinical team directly (although in practice, this did not occur during this study).

If a participant wished to raise any concerns or make a complaint, they were advised to contact the Patient Advice and Liaison Service (PALS); the telephone number was provided at the bottom of the patient information sheet. PALS is an independent service provided by the NHS and not connected in any way to the research study.

4.14 DATA MANAGEMENT

Patient-identifiable data were collected and stored in accordance with Caldicott principles and the Data Protection act. All interview transcripts were pseudonymised and patient data were stored electronically on NHS computers or encrypted media, in accordance with local IT policies. Paper records were securely stored in the study site file and access was restricted to those directly involved with the qualitative study.

CHAPTER 5: RESULTS: STUDY FEASIBILITY AND PRELIMINARY QUANTITATIVE DATA ANALYSIS

5.1 INTRODUCTION

In the following chapter, quantitative study data from a single site (UHND) will be presented and analysed, along with the outcome of pre-study site feasibility assessments and patient-public involvement consultations.

Data presented here represent interim results from a single trial centre (University Hospital of North Durham (UHND)) nested within the large multi-centre CapaCiTY 02 trial . The purpose of this quantitative data analysis is to assess the feasibility of the CapaCiTY 02 study by looking at recruitment rates, completeness of data collection, and preliminary descriptive analysis of the primary study outcome (difference in mean PAC-QOL between HV and LV groups after 3 months). Calculating the standard deviation allows the appropriateness of the sample size calculation (which assumed an SD of 1) to be assessed. Although this study was not designed *a priori* as a feasibility study, it is nonetheless instructive to present data in this way in order to inform current and future conduct of the study nationally.

5.2 PRE-STUDY SITE FEASIBILITY ASSESSMENT

Before recruitment commenced, feasibility questionnaires were sent out to 13 prospective sites. Responses were received from nine of these. As expected, there were considerable variations in practice regarding precisely how patients are trained to use the irrigation. Although most centres were fairly consistent in having an initial training session of 30-60 minutes, the precise content of this session varied. The

original proposed training regime suggested that the patient should demonstrate irrigation in the clinic under the guidance of the irrigation nurse. However, many centres said they did not have the resources for this and that it did not form part of their usual practice although many centres did have the patient set-up the device in clinic to show that they could use it. Follow-up methods and timings varied, with telephone follow up being the most common approach, varying between 24 hours and 4 week from the initial session. Some centres also offered patient-led or flexible follow up.

Taking these variations into account, it was not possible to design a standardised irrigation training regime that met the needs and resource issues of each centre. Therefore a flexible approach was adopted, as outlined in Chapter 3, section 3.7.1, with the requirement for the patient to use the irrigation in clinic removed. However, if the participating centre had the resources available and the patient wished to do this, then this demonstration was permitted. Also, each centre used different irrigation systems which reflected local availability and prescribing policies, so therefore the decision was made that any high-volume system could be used, provided it had a similar mechanism of action. There was reasonably good consensus that the rescue therapies were sensible, however greater flexibility was incorporated to allow patients to use additional laxatives and prokinetics during follow up if their symptoms were severe despite irrigation and the rescue therapy.

5.3 PRE-STUDY PATIENT PUBLIC INVOLVEMENT (PPI)

Before the study commenced, thirteen patients currently attending the constipation clinic were given a questionnaire about the proposed study design, with a view to

ascertaining their views and opinions about key aspects of the proposed trial design. These patients were not necessarily to be considered for participation in the trial, and were not screened to see whether they were eligible. Regarding random allocation of the irrigation system, twelve out of thirteen patients were willing in principle to accept either study intervention. Also, 10 patients were happy in principle to accept the restriction in laxative use. However only seven patients said they would be happy to wait for three months before switching treatments; following some discussion between members of the research team and the Chief Investigator, it was decided that the three-month period was necessary to obtain meaningful outcome data and therefore retained. It is however acknowledged that this represents a compromise between scientific rigour and patient acceptability. Overall, nine of the patients said they would participate in the study as described, with three saying they would not, and one patient unsure whether they would or not.

Additionally, nine patients were given the study documents (Patient Information Sheet, Patient Journal, Irrigation Journal and Patient Diary) and asked to comment on them, with five responding. Their comments are summarised below:

- *Patient 1: Happy with all documents; they would like a face-to-face explanation of how to use everything*
- *Patient 2: Happy with the diaries and patient information sheet. They would like something added concerning eating and drinking patterns and their effect on symptoms*
- *Patient 3: Happy with all documents*

- *Patient 4: Regarding the patient information sheet, they would like the flowchart moved nearer the beginning of the sheet, before the main description of visits. They would like more information on the differences between systems. Regarding the Irrigation journal, they felt this should be daily rather than weekly.*
- *Patient 5: Would like 'less wordy' section on purpose of study in the patient information sheet, and felt bullet points should be used, rather than paragraphs. They felt the journal should include dietary information also. They described the irrigation journal as 'excellent', but would like a box for duration and timing of irrigation.*

On the whole, these were taken to be positive comments regarding the study documents. There were no major areas for improvement consistently highlighted, and collecting data on dietary factors was felt not to be relevant for this study.

5.4 PRE-STUDY CONSTIPATION RESEARCH ADVISORY GROUP (CRAG) REVIEW OF ASSESSMENT QUESTIONNAIRES

Of the six patients invited to participate in this seminar, three were able to attend. Additionally, the questionnaires were completed by three investigators (a consultant, a research nurse and a research fellow). Each participant recorded the time taken to complete each questionnaire, and the mean time for completion of each questionnaire was calculated (see table 1 below). Three participants completed scores for relevance, and the mean scores are given below. It should be noted that the baseline questionnaire booklet was amended in light of operational problems encountered (see section 5.5 below); the booklet reviewed by the CRAG was the

original one, hence the differences between the questionnaires listed below and the baseline assessments outlined in Chapter 3.

It can be seen from the table below that the aggregate time taken to complete the booklet was around 40 minutes. Perception of ease and relevance of each questionnaire was very variable, with the short outcome questionnaires (PAC-SYM, PAC-QOL and EQ-5D-5L) being seen as relevant and straightforward to complete, scoring 1-2 for each domain; however others were deemed to be either more difficult (MYMOP, CC-BRQ, Cleveland Clinic, ROME III), or less relevant (MYMOP, PHQ-15, GAD-7, PHQ-9, St Marks, ROME III, Joint Hypermobility).

Table 1: Ease, relevance and time taken to complete each questionnaire

Questionnaire	Time (mins)	Ease 1-5*	Relevance 1-5*
PAC-QOL	02:48	2	2
PAC-SYM	01:18	1	2
EQ-5D-5L	01:04	1	2
MYMOP 2 Initial	02:15	3	3
PHQ-15	02:15	2	3
GAD-7	00:37	1	4
PHQ-9	00:44	1	3
CC-BIPQ	00:54	2	2
CC-BRQ	02:10	3	2
Cleveland Clinic	01:47	3	2
St Marks	01:01	2	3
Rome III	04:30	4	3
Joint Hypermobility	00:33	1	3

**scored from 1 (very easy/relevant) to 5 (very difficult/not at all relevant)*

Although this was a short exercise involving a small number of patients and investigators, it nonetheless shone some light on the participants' experiences of filling out the questionnaires, and helped to guide some amendments to the study, as outlined in the following section (5.5).

5.5 OPERATIONAL PROBLEMS ENCOUNTERED FOLLOWING STUDY COMMENCEMENT

5.5.1 INVEST

There were several difficulties encountered surrounding the logistics of completing the pre-treatment radiophysiological investigations (INVEST) within the timeframe specified in the study protocol (i.e. within 8 weeks of informed consent). Originally, it was suggested that INVEST should include fluoroscopic defecation proctography and high-resolution anal manometry, as well as a transit study. However, many study sites (including Durham) did not have the required equipment to perform high-resolution manometry, meaning that this was not possible.

Additionally, it was felt that performing defecation proctography on every participant was impractical, as it would place undue pressure on radiology departments and cause delays in recruitment. It was felt that any scientific benefit gained from performing this examination was likely to be minimal, and did not justify the additional radiation exposure or expense incurred. Therefore the decision was taken to revise the requirements for INVEST to allow both standard and high resolution manometry, according to local availability, and to remove the requirement for defecation proctography. As recruitment had already commenced at this point, this required a major protocol amendment (as outlined below in section 5.6.1)

5.5.2 Completeness of data and outcome assessment

Initial experience with the first three patients recruited at UHND revealed some problems with outcome data being incomplete. This included missing answers on the concealed primary outcome questionnaire. In response to this, the issue was raised with the chief investigator and it was agreed that the primary outcome questionnaire (PAC-QOL) should be inspected briefly by a member of the research team in order to ensure completion before being sealed in the envelope. This was felt to be a reasonable compromise between the requirement that data be concealed adequately and ensuring data are as complete as possible.

Further issues surrounded the patient-held documents; the diaries were sometimes omitted or returned with missing answers, as were the journals (irrigation journal and patient journal). There was scope within the study protocol for diaries to be completed from the day of the visit and returned by post if they had not been filled in beforehand, however on some occasions this was not done. This is analysed in greater detail in section 5.9 (also see table 3).

5.6 PROTOCOL AMENDMENTS MADE IN RESPONSE TO CHALLENGES

5.6.1 Changes to INVEST

As detailed previously, amendments were made to the INVEST radio-physiological investigations performed before treatment was started. It was decided that anorectal physiology was important scientifically in order to evaluate whether differences in rectal sensation, manometry or balloon expulsion test results are predictive of success of irrigation therapy. However, it was decided that high-

resolution methods did not add to this in a significant way, especially in view of the significant operational difficulties encountered in securing funding for procuring this equipment for sites not currently using it as standard. The transit study was felt to be useful and easy to implement with minimal costs and only slight radiation exposure; it also represents standard care for chronically constipated patients.

However, the role of barium proctography was less clear cut; it was decided not to perform this routinely as it represented a significant cost to the NHS and also a significant radiation exposure for the patient, as well as causing a delay in starting treatment as waiting lists for the test were long (4-8 weeks). Thus this test was removed from the study protocol.

Another change was to extend the time window for using results from tests done before study recruitment from 6 to 12 months. This reduced the need for repeated investigations and will not affect the scientific value of the study given the chronic, stable nature of the condition being studied

5.6.2 Changes to questionnaires and follow up duration

As previously noted, there were problems with incomplete and missing answers on questionnaires. Also, there was concern expressed about the burden of measurement and study duration, and whether this was causing problems with study recruitment and retention of participants. Following discussion between investigators and in light of patient feedback (see CRAG results described previously), the number of questionnaires was reduced at baseline, three and six months. The one-month short outcome assessment was retained as it provided

useful early outcome measurements in patients who discontinue treatment early, or are lost to follow up.

In order to ensure completeness and accuracy of outcome data collection, it was agreed with the chief investigator that the PAC-QOL questionnaire could be checked by a member of the research team before being placed in the sealed envelope, as long as the total score was not calculated and the participant was not influenced in any way while completing it (other than by being encouraged to fill in missing answers). This ensured that outcome data were as complete as possible without compromising the scientific integrity of the study.

A further major change was to shorten the total study follow-up period from 24 months to 12 months. The aim of this change was to reduce the commitment being asked of participants to a more reasonable level, thereby aiming to increase recruitment and retention of participants.

5.6.3 Online data entry (REDCAP)

The revised protocol included a mechanism allowing patients to complete their patient diaries and outcome questionnaires online (See chapter 3). This enabled participants who chose this option to record outcome data in this way, and complete the rest of their follow up by telephone. Out of 19 participants, 8 (42%) preferred to conduct follow up in this way , and it also ensured completeness of data collection by preventing participants from moving to the next questionnaire if questions were left unanswered.

5.6.4 Change to randomisation time point

Operationally, it was found to be challenging to randomise patients and then immediately start irrigation. Some sites reported difficulties in obtaining enough equipment to start treatment straight away. Therefore, randomisation was instead performed at the first study visit, immediately after informed consent and completion of the baseline outcome assessment questionnaires.

5.7 RECRUITMENT AND RETENTION OF PARTICIPANTS TO CapaCiTY 02

As of the 18th August 2016, six sites are open to recruitment nationally. A total of 23 participants have been recruited across these sites. Of these, 19 were recruited at a single site (University Hospital of North Durham). Recruitment by site is shown in figure 1. This is a much slower recruitment rate than is required in order to complete recruitment within the planned time frame (see figure 2 below). Reasons for this will be explored in the following sections, and proposed strategies for improving this will be discussed in chapter 7.

Figure 1: CapaCiTY 02 enrolment by site

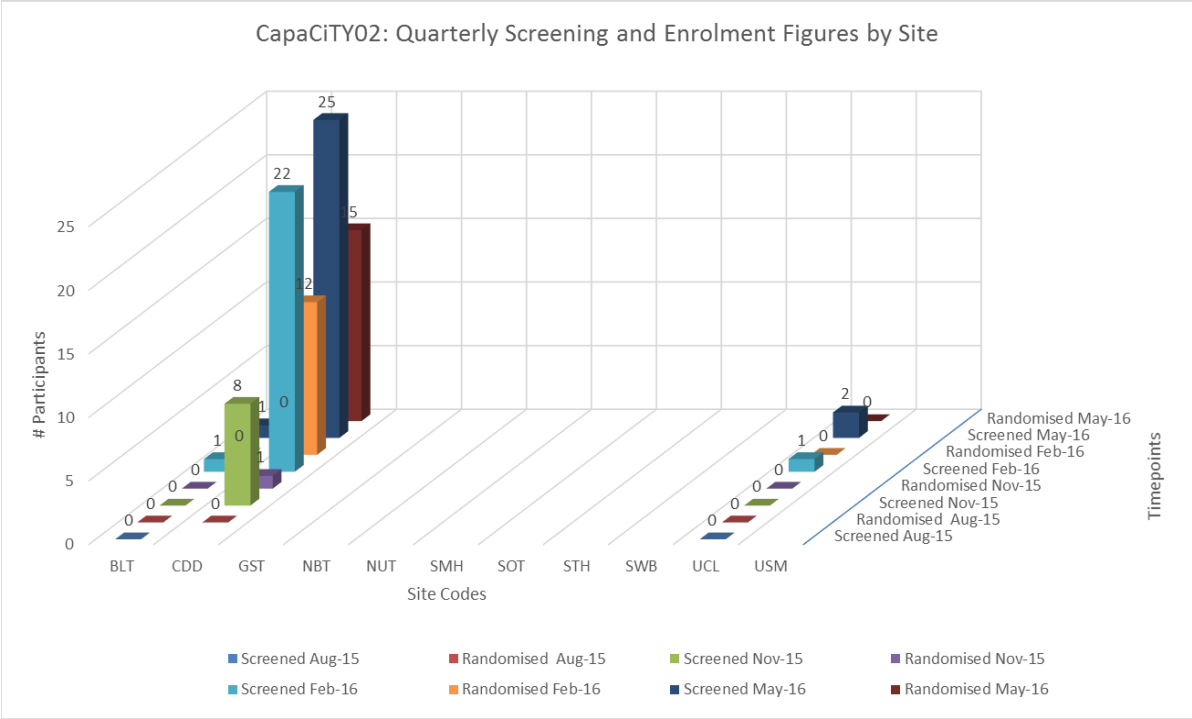
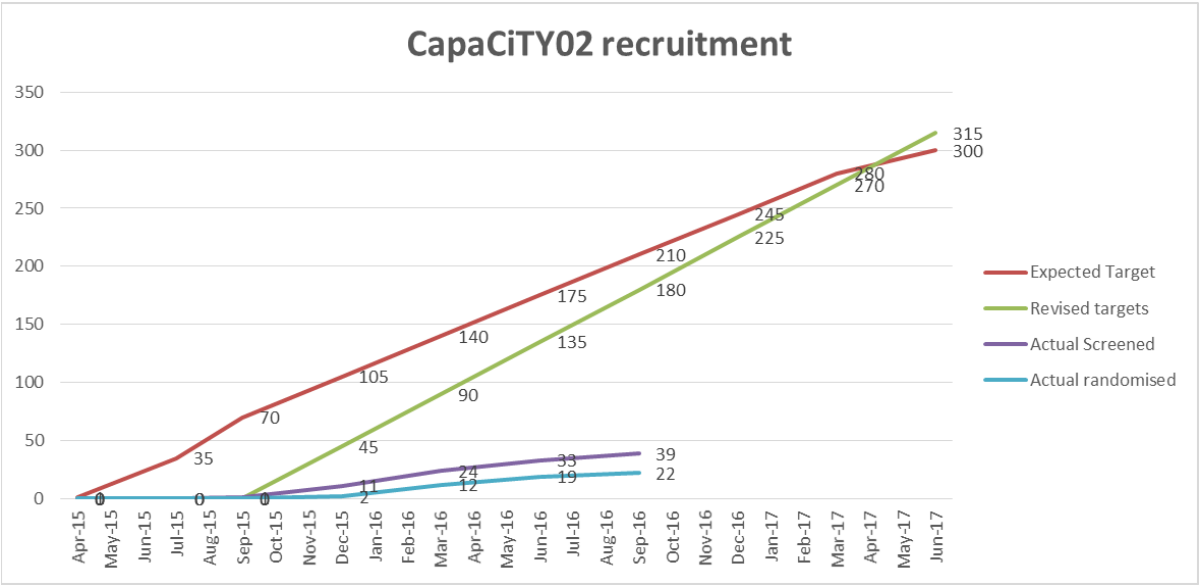


Figure 2: CapaCiTY 02 recruitment (expected and actual)



5.8 RECRUITMENT AND RETENTION OF PARTICIPANTS AT UNIVERSITY HOSPITAL OF NORTH DURHAM (UHND)

Recruitment to the study at the University Hospital of North Durham commenced in September 2015. Additionally, two other sites opened to recruitment a month before this. Between 1 September 2015 and 31 July 2016, 33 patients were screened at UHND. Of these, 19 consented to participate in the study. This gives a mean of 1.9 patients recruited per month. The ratio of those enrolled to those screened is 0.58. The monthly screening and recruitment figures are given in table 2 below. As of 18 August 2016, 2 patients have withdrawn from the study (elective withdrawal – reasons unknown).

This demonstrates that the original recruitment target of 1 patient per month per site is achievable. However, following delays to study commencement and poor recruitment at other sites, this target was revised to 2 patients per site per month in order to complete recruitment on schedule. This revised target is also being achieved at UHND. The projected withdrawal and loss to follow up rate was estimated at 10%; the rate of 2 withdrawals from 19 participants (10.5%) is consistent with this. Also, the predicted ratio of those enrolled to those screened of 0.5 appears to be a reasonable estimate in light of the observed ratio of 0.58 seen at Durham.

Table 2: Screening and enrolment at UHND

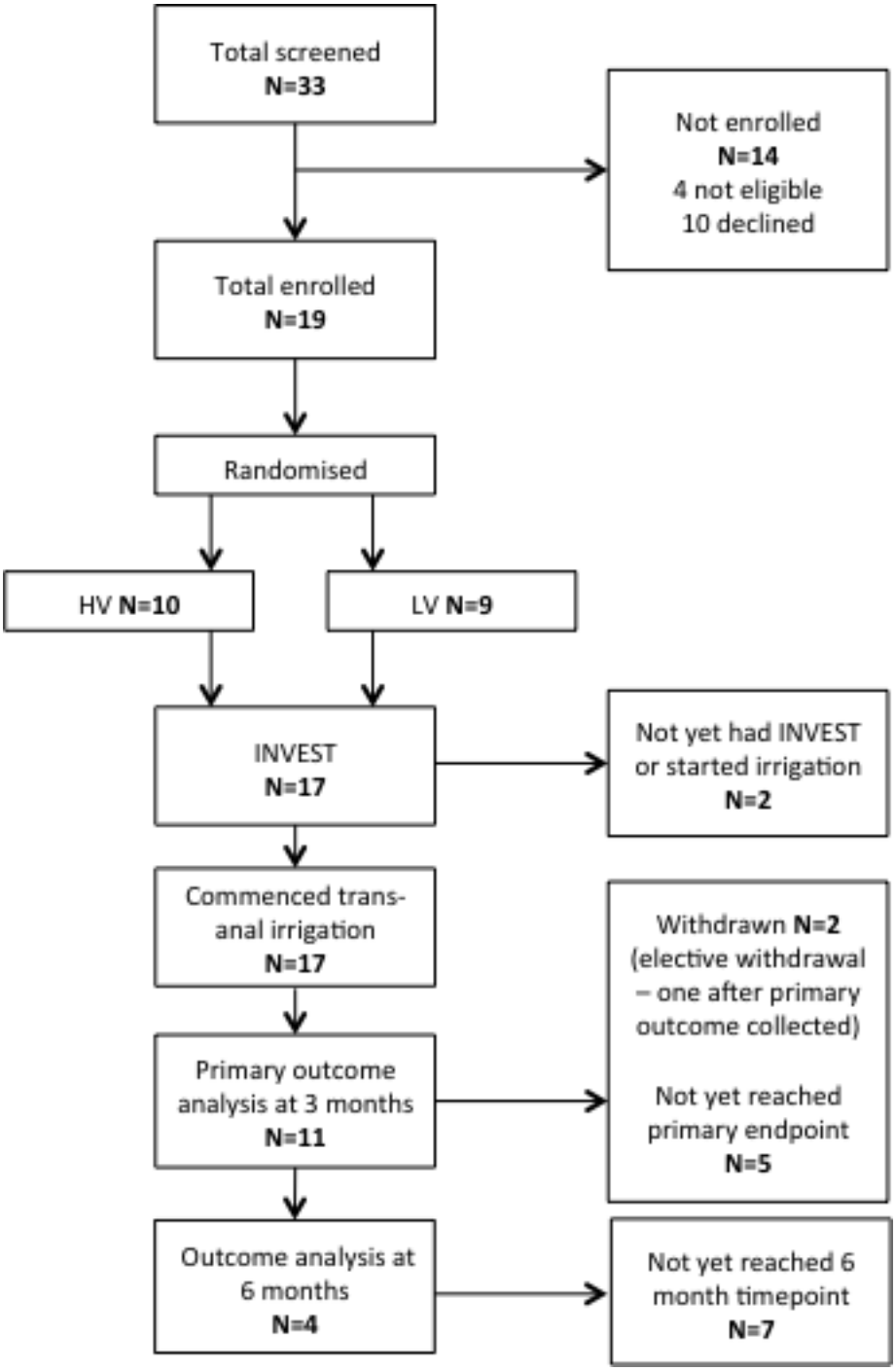
Month	Screened (n)	Enrolled (n)	Ratio enrolled/screened
Sep 2015	1	-	-
Oct 2015	3	1	0.33
Nov 2015	4	1	0.25
Dec 2015	4	3	0.75
Jan 2016	3	3	1.00
Feb 2016	3	1	0.33
Mar 2016	4	3	0.75
Apr 2016	2	2	1.00
May 2016	1	1	1.00
Jun 2016	4	2	0.50
Jul 2016	4	2	0.50
Total	**33**	**19**	**0.58**

5.9 DEMOGRAPHICS OF STUDY PARTICIPANTS AT UHND

The numbers of patients screened and enrolled at UHND are given in the CONSORT diagram below (Figure 1). There were 19 participants recruited at UHND; the mean and median age was 43 years (range 23 – 65 years). There were 18 female participants and one male. At the time of writing, 11 participants have had their three month primary outcome visit (including one patient who later withdrew from the trial). A further 6 participants have not yet reached this outcome time point, and a further patient withdrew before reaching this. Therefore 17 participants are

continuing with participation currently. The study continues to recruit actively at a mean rate of 1.6 participants per month. With the agreement of the study team, the following data were extracted from the trial database on 18 August 2016.

Figure 3: Consoldated Standards of Reporting Trials (CONSORT) diagram for CapaCiTY 02 at UHND



5.10 COMPLETENESS OF DATA COLLECTION

The CapaCiTY 02 study involves the collection of a great deal of outcome data at the time points previously described, in the form of case report forms (CRF), questionnaires and patient symptom diaries. This represents a potentially onerous burden of measurement for participants. As part of this feasibility analysis, it is

important to evaluate completeness of data collected to assess whether the outcome measures used are appropriate and achievable.

Table 2 below illustrates the proportion of questionnaires, diaries and investigations for each time point that were complete, partially complete, or not completed. Data are presented for the 19 participants who had had at least baseline data collected (as of 18th August 2016). Of those, 17 had reached the INVEST visit, 15 had provided outcome data at 1 month, 11 provided 3-month data, and 4 had reached the 6-month data collection visit.

It can be seen that the primary outcome questionnaire (PAC-QOL) has been collected for between 93% and 100% of participants at each time point. The one occasion where the PAC-QOL was not done was for a participant who did not attend the 1-month visit, therefore the time point was recorded as missing. Of the baseline PAC-QOL questionnaires, two had missing answers and a further 2 were not available for analysis due to the data not being present on the central database at the time of writing. Similar rates of completeness were seen at 1 and 3 months. Missing answers for PAC-QOL is not critical since the questionnaire was designed to allow for this, as the total score (014) is the sum of the answers given divided by the number of questions answered.

The diaries have been less completely recorded; at baseline, 4 (21%) diaries were not completed at all, and a further 4 had at least one missing answer. A similar proportion of diaries were not done at three months (4 diaries, 36%). A at six months three of four participants (75%) had returned a diary, with two (50%) being completely filled in with no missing answers.

Table 3: Completeness of investigations and outcome data

	Baseline PAC-QOL	Baseline questionnaires	Baseline Diary	ARP*	TS**	1-month PAC-QOL	1-month questionnaires	3-month PAC-QOL	3-month questionnaire	3-month diary	6-month PAC-QOL	6-month questionnaire	6-month diary
Complete (%)	15 (79)	12 (63)	9 (47)	12 (71)	17 (100)	12 (80)	12 (80)	10 (91)	10 (91)	5 (45)	4 (100)	3(75)	2 (50)
1 or more missing answers (%)	2 (11)	5 (26)	4 (21)	NA	NA	2 (13)	2 (13)	1 (9)	1 (9)	2 (18)	0 (0)	1 (25)	1 (25)
not done (%)	0 (0)	0 (0)	4 (21)	5 (29)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)	4 (36)	0 (0)	0 (0)	1 (25)
not available (%)	2 (11)	2 (11)	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

**Ano-rectal Physiology; **Colonic transit study*

Regarding pre-treatment investigations (INVEST), all 17 participants who have reached this time point have had a transit study. Ano-rectal physiology was performed in 12 (71%) participants; the reason for the omission of this test in 5 cases was that this investigation became unexpectedly unavailable for a time. Following discussion with the chief investigator, it was decided that the physiology testing could be omitted for participants already recruited to the trial, so as to minimize delay in treatment. This was recorded as a protocol violation.

5.11 PRIMARY OUTCOME DATA: INTERIM RESULTS

In the following section, a descriptive analysis of the primary outcome (PAC-QOL at 3 months) is presented. Data are from the 11 participants who have reached this point in the study. This includes 10 female participants and one male. Of these, 6 were randomised to high-volume irrigation and 5 to low-volume irrigation.

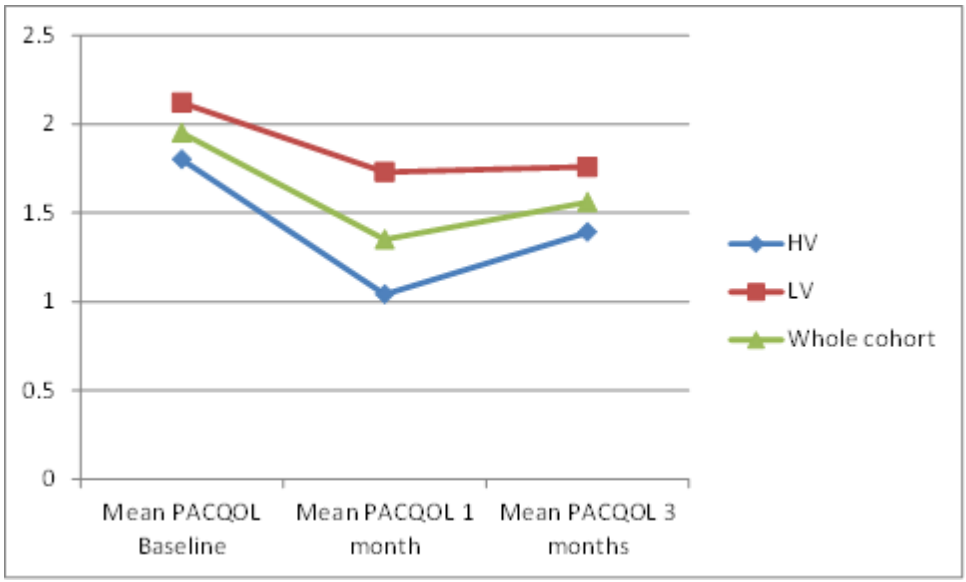
For the whole study population, mean PAC-QOL fell from 1.95 at baseline to 1.56 after 3 months, a mean reduction of 0.39 (see table 3 and figure 2 below). The standard deviation of 0.44 is lower that the SD of 1 used in the power calculation, suggesting that the sample size is sufficient to detect a 10% (0.4 point) difference in reduction in PAC-QOL between the groups. In this population, the reduction in PAC-QOL at three months was 0.41 for high-volume users and 0.36 for low-volume users, a difference of 0.05 in favour of high volume irrigation. However, the numbers in this feasibility study are too small for meaningful conclusions regarding comparative efficacy of each system to be drawn. It should also be noted that one of the five LV participants (20%) switched to high-volume irrigation after 1 month due to patient-perceived lack of efficacy. This was recorded as a protocol deviation, and the data

included in the low-volume data set in accordance with the principle of analysis by intention to treat.

Table 4: Mean reduction in PAC-QOL by system

	Mean (SD) PAC-QOL score			
Irrigation system	**Baseline**	**1 Month**	**3 Months**	**Reduction**
High Volume	1.8 (0.43)	1.04 (0.49)	1.39 (0.60)	0.41 (0.39)
Low Volume	2.12 (0.80)	1.73 (0.81)	1.76 (0.78)	0.36 (0.54)
Whole cohort	1.95 (0.61)	1.35 (0.72)	1.56 (0.60)	0.39 (0.44)

Figure 4: Mean PAC-QOL by system

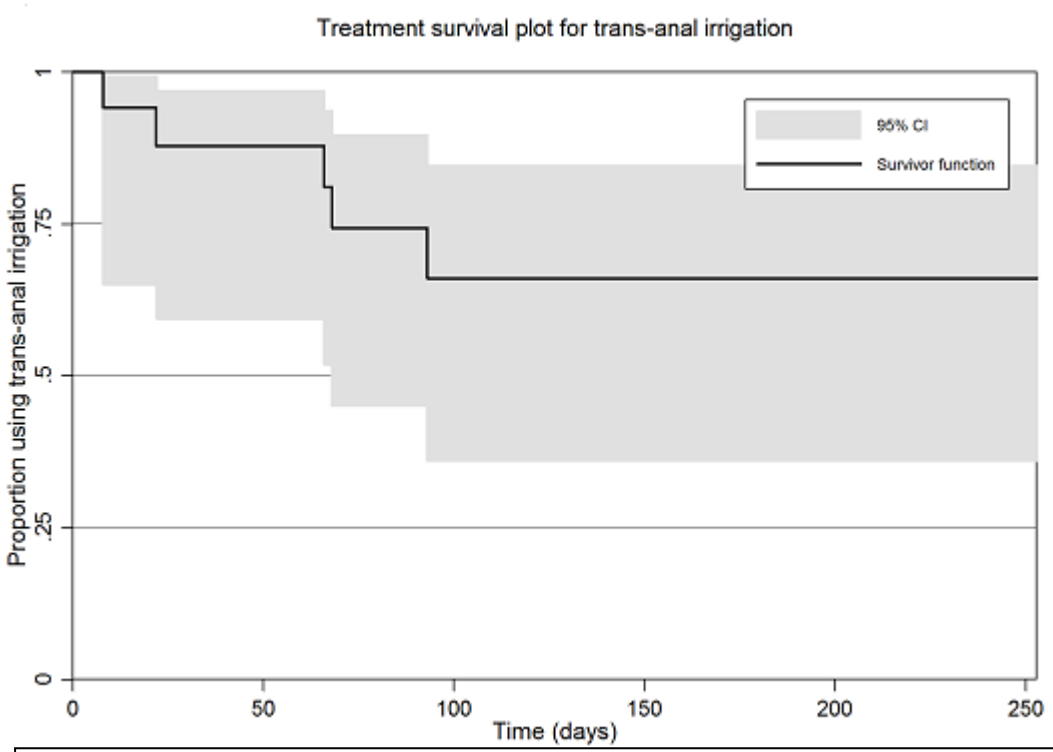


5.12 SURVIVAL DATA (CONTINUATION OF BENEFIT): INTERIM RESULTS

As previously noted, 17 study participants had commenced trans-anal irrigation therapy as of the 18th August 2016. Although these numbers are small, thereby introducing considerable uncertainty into any statistical interpretation, it is instructive to present the interim data for survival (i.e. continuing use of treatment) here. This may be considered to be a surrogate marker for treatment efficacy as the nature of the treatment means that participants will likely not continue to use it if they are not deriving some benefit.

Data are presented for the whole cohort, and are not separated out into high- and low-volume users. This is consistent with the analysis plan for the CapaCiTY 02 study. As on the 18th August 2016, 5 patients (29%) had discontinued treatment, after a mean time of 51 days (SD 35.2) Figure 5 shows a Kaplan-Meier survival plot with 95% confidence intervals:

Figure 5: Treatment survival plot for trans-anal irrigation



Kaplan-Meier survival plot showing the proportion of participants continuing with treatment over the course of the study (solid line) with 95% confidence interval (Shaded area)

It can be seen from the wide CI and small numbers that there is considerable uncertainty in this analysis: Clearly more data are needed in order to build a complete picture of the true duration of benefit. However, this interim analysis is instructive as it suggests that the majority of those who discontinue treatment do so early (before 3 months of use). Combined with the fact that a further two patients switched therapy before three months (as detailed previously), this indicates that the one-month data collection time point is justified and useful as it allows data capture in these participants while they are still using their allocated system. Of the 9 participants allocated HV, 4 (44%) discontinued compared to 1 of the 8 allocated LV (12.5%). Of the 5 patients who discontinued in total, one reported persistent PR bleeding, another reported incomplete evacuation and lack of treatment effect. A

further patient reported pain and bloating, as well as lack of efficacy and a sensation of incomplete evacuation, and found that the treatment was not acceptable. Another participant gave excess pain, defecation at low volumes, and increased frequency as reasons for stopping. The final participant withdrew from the study without giving specific reasons for this.

Additionally, four patients out of 17 switched therapy in this time period (23.5%). All of these were participants who started with low volume irrigation (50%). Mean time to switching treatment was 67 days (SD 29.6).

5.13 SAFETY OF TREATMENT AND ADVERSE EVENTS

Data for adverse events are first collected at the 1-month visit. At the time of data analysis, 15 patients had reached this time point and therefore had provided data for analysis.

5.13.1: Serious Adverse Events (SAE)

There have been two unrelated Significant Adverse Events so far in this study. Both involved the same patient. This patient underwent elective surgery (planned parotidectomy), which necessitated admission, and also had a hospital admission for an acute exacerbation of constipation symptoms. After discussion with the study PI and having been reported to the CI as per protocol, it was agreed that these were unrelated SAEs and that no further action needed to be taken. The participant continued with the study.

5.13.2: Adverse Events (AE)

Of the 15 participants from whom 1 month data has been collected, 11 (73%) described one or more related adverse events. Of the remaining 4 participants, three (20%) reported no AE and the final patient did not attend the 1-month visit, so data are not available. Table 5 below summarises the rates of the observed AEs.

The overall rate of AEs is high in the study population. This is consistent with the current evidence, which suggests minor side effects are commonplace (see Chapter 3: Systematic Review). However, the only SAEs seen in this study so far have been unrelated to the trial therapy, and there has been no significant harm to participants as a result of trial participation. It can therefore be suggested, based on this feasibility study, that trans-anal irrigation therapy is safe and that there have been no significant safety concerns that would lead to the termination of the trial. The prospective tracking of AEs is an important secondary aim of the CapaCiTY 02 study, as there is a lack of firm evidence in this area as detailed in Chapter 3.

Table 5: Adverse Events

Adverse Event	N (%)
Anal pain	3 (20)
Nausea	1 (7)
Abdominal pain	6 (40)
PR bleed	4 (27)
Bloating	2 (13)
Lethargy	1 (7)
Pain (not specified)	1 (7)
Incontinence /leakage	1 (7)
Spillage of water	1 (7)
Urgency	2 (13)
Increased frequency of bowel motions	1 (7)
Headache	1 (7)
Sacral discomfort	1 (7)

Due to the low numbers, further statistical analysis was considered inappropriate. The above analysis is sufficient to evaluate the feasibility of the study and to comment upon the appropriateness of the outcome framework. This discussion will be expanded upon in Chapter 7.

CHAPTER 6: QUALITATIVE STUDY RESULTS AND DATA ANALYSIS

6.1 INTRODUCTION

The qualitative research component of this study aimed to define the essence of the lived experience of study participants of learning and using trans-anal irrigation therapy. A transcendental phenomenological methodology was employed to achieve this was through the use of semi-structured interviews with existing study participants at two time points in the study; after completion of irrigation training at 1 month, and after 6 months of study participation. This allowed participants to describe their experiences of the training process as well as home use of the irrigation. Interviews were transcribed verbatim and key themes identified. Analysis of these themes was performed using a phenomenological framework, in which the experiences of individuals who experienced trans-anal irrigation therapy were captured and analysed to produce a description of the essence of the participants' lived experiences.

In order to capture as broad a range of experiences as possible, purposive sampling was used at each time point, with the aim of ensuring that a diverse range of demographics and outcomes was represented. A more detailed description of the study aims and methods, as well as the theoretical framework and sampling grids, can be found in chapter 4. The following chapter outlines the key themes that emerged for each time point.

6.2 STUDY SAMPLE 1: AFTER COMPLETING IRRIGATION TRAINING (1-MONTH VISIT)

A total of five study participants consented to a single interview after completing training in anal irrigation as laid out in the quantitative methods chapter (chapter 3). The first eight participants recruited to the quantitative study were considered for recruitment into the qualitative study. Of these, one participant had already completed irrigation training more than one month previously and was therefore ineligible. Another participant did not wish to participate (no specific reason given), and another could not spare the time for an additional study visit. The remaining five participants agreed to be interviewed and were recruited to the study. There were four female participants and one male. Three participants were aged under 40, two were aged over 40. Three participants had been using high-volume irrigation and two were using low volume. All interviews were conducted face to face. After each interview, the transcripts were read by two researchers (CE and HC) and it was agreed that data saturation had been reached at this point. In the following, each participant has been assigned a letter (A-E), and this is used alongside the irrigation system ('HV' or 'LV) to attribute direct quotations to each participant while preserving their anonymity. For example, [A HV] is participant A using high-volume irrigation.

6.2.1 CODING AND THEME IDENTIFICATION

Each transcript was studied line by line and a total of 80 key words or phrases were identified. These were then grouped together and the following key themes emerged; 'Experience of the training process'; 'Pre-treatment expectations and reality'; 'Attitudes towards, and experience of, using irrigation'.

6.2.1.1 Theme 1: Experience of the training process.

Within this theme, key aspects were the support process infrastructure, the behaviour of and support from healthcare professionals (the irrigation nurses in particular), and participants' attitudes towards them. Several participants expressed a degree of anxiety or discomfort about starting irrigation, as well as undergoing the pre-treatment investigations, but the contact with the healthcare professionals helped them overcome this. One participant stated;

"…I think that the training felt not as intrusive as I thought it would be, the questions weren't as embarrassing, um, and I didn't need to sort of go into details that I found uncomfortable, but we talked about enough past history to reach an understanding as to where I was and what I needed to do in the future to help my situation. So yeah, I quite liked the way that we talked about it, and it put me at ease" [B LV]

Others reported;

"…And I felt comfortable as well, and sometimes you think, oh, bowels, you can't talk about it, it's not a subject to talk about, but I felt comfortable and no embarrassment or anything. I think that was positive, I had a good rapport with all the team to be honest, everybody's been great." [D HV]

"I was pretty nervous, but when I came I was put at ease by the nurses, doctors… I was quite pleased with the treatment."[A HV]

"I was quite happy to go ahead and happy with the situation, and felt comfortable with the staff and the whole set-up."[D HV]

The on-going support from irrigation nurses was also highly valued by participants. Participants expressed reassurance at having a point of contact that they could ring up between sessions. This seemed to be valuable even if the participant did not need to contact the nurse. One participant commented;

"I think that at every stage, what contact with staff has done has provided reassurance that this is not an uncommon condition, and that there's no one right way to deal with that, so there's been flexibility and people have listened in a really kind of respectful way, to the problems that I've had, and been really kind of helpful in offering solutions"

"I think the opportunity to gain telephone support – I haven't done that apart from the scheduled one, but I think that's available, it's helpful, and it's reassuring to know that advice is there" [C HV]

Other participants also highlighted the support from nursing staff as being valuable. One of these said:

"…she [the irrigation nurse] *was very thorough, she encouraged me to ask questions, so, and reassuring and giving me her phone number and things so I knew if I had any problems there's somebody on the phone so it was reassuring, so I think that was positive, knowing that." [D HV]*

These comments highlight the importance of the nurse-patient relationship in successful irrigation training. One dimension of this theme is the dynamic that gender differences play in this relationship, and the perceived effect that this can have on training. The study site has only female irrigation nurses; the only male

participant to be interviewed emphasised that he would have felt more at ease if he had been trained by a male nurse, and he perceived a negative effect on his training experience as a result of the lack of choice. He was offered the opportunity to demonstrate the device in clinic (which is a common practice at the study site), but declined this, stating:

"…she [irrigation nurse] *says if I could, she wanted me to try it, do a trial, in the hospital but I didn't want to do it because it was a woman, I felt a bit, er, a bit shy, as it were." [A HV]*

This has important implications, as some participants found the opportunity to try the system out in clinic to be a very helpful aspect of training although other (female) participants found it less helpful. One participant found it very helpful, describing it as "a really useful learning model". She went on to explain;

"… it's an odd kind of experience so you're not quite sure what should be normal about the procedure so the opportunity just to, to kind of shout through the door and say 'is this what I'm supposed to be doing, is this right?' was really useful." [C HV]

In her opinion, she would have struggled with using the device a lot more had she not been able to demonstrate it in clinic;

"…I think it was extremely valuable. I think it goes to show that the couple of problems I had later… you're trying to take in a lot of information all at once with a procedure that feels really unnatural, so I think there's lots of kind of sequential things that could go wrong… not wrong, but just kind of, are not entirely clear. So

even with all that really good explanation and opportunity there was still a lot of confusion for a wee while... if I hadn't had that I think it would have been much worse" [C HV]

However, another participant was offered this but declined, preferring to miss out this step and carry out the first irrigation at home. This was due to issues around embarrassment and privacy, as well as feeling that it would be straightforward enough to do at home:

"…it's still something that I feel a bit embarrassed talking about, or doing, so I just preferred to do it at home" [B LV]

This illustrates the importance of flexibility in the training process, and that it is essential to elicit a patient's feelings and concerns in order to maximise the effectiveness of the training.

6.2.1.2 Theme 2: Pre-treatment expectations versus actual experiences

A common theme across all the interviews was the comparison and contrast between participants' pre-conceptions about undergoing investigations and treatment, and the experience of doing so.

Before beginning training, patients enrolled in the CapaCiTY 02 study underwent a series of radiological and physiological investigations, as outlined in Chapter 3. These included a colonic transit study (plain abdominal X-ray 5 days after ingesting marker capsules), and anorectal physiology studies. These include measurement of anorectal pressures and sensitivities using a balloon catheter inserted anally. A

defecating proctogram originally formed part of this package but was removed shortly after recruitment began.

The prospect of undergoing the investigations was a source of anxiety for some participants, particularly the proctogram and the anorectal physiology. It is interesting to note from the following excerpts that, while several of the participants interviewed expressed anxiety beforehand, the actual experience of using the treatment was perceived more positively.

One participant stated "I thought it would be quite scary but it was fine". When asked to elaborate on this, they replied;

"It was just the test… …the suitability test for it, I wasn't sure what they were going to be, and all these monitoring and things like that so I was a bit apprehensive about that but there was no issue with it at all really." [E LV]

Another patient was similarly anxious about undergoing investigations. They did not have to have the anorectal physiology, but anticipating this had clearly been a source of worry;

"I was apprehensive, and I was also thinking about what the tests were possibly going to be, but then when we were able to bypass that test, I thought 'phew!' we can go straight on to the irrigation." [D HV]

Participants also had preconceptions about the nature of irrigation treatment and this was explored in the interviews. These ideas were formed from patients' previous experiences of 'colonic irrigation' therapy (colonic hydrotherapy provided through private complimentary therapy clinics), and from information obtained from other

sources such as the media, as well as the trial patient information sheet. Preconceptions included feeling that the procedure would be difficult to do, or that it would be messy or uncomfortable:

"I felt a bit nervous about doing the irrigation because as I say I've done colonic irrigation in the past, but since I've had my two children that was quite sore, on the second of the three occasions it was pretty sore, so I put that down to, like, childbirth and repercussions after that, so I was a bit worried that it would be sore, but it was fine" [B LV]

"I thought it would have been hard, I'd never done anything like that before, but I, I tried it, ….really…really good, I felt great with it." [A HV]

"Totally different to what I thought. Watching these television programmes where people have the irrigation and you're thinking 'oh, this is going to be really messy', but it wasn't. I don't know what I was expecting, lots of stuff to come away and thinking 'oh, there's going to be mess, lots and lots of mess' but it's just the water that's gone in comes back out, so that was a bit of a shock, cos I was thinking 'am I doing it right?' cos it just seems to be clear water coming back and obviously <research nurse> has explained yeah that's quite natural, so…" [D HV]

One patient expressed disappointment that they had had to start irrigation therapy at all, commenting that they already felt they were 'not normal' as a result of their condition, and that having to do something 'mechanical' like trans-anal irrigation emphasised and drew attention to this in an uncomfortable way:

"I suppose just psychologically, you know, living with this condition kind of over the years, you already feel that things are not normal, that your body's not working the same as other people's are, so I think that having to do something to mechanical feels… it feels disappointing, it feels like actually, why is my body not kind of responding the way that it should. So there's a bit of a sense of disappointment that it has come to the fact that you have to, you know, do something extra." [C HV]

This participant expressed a preference for taking medication rather than using the irrigation; when asked if they felt their condition was being 'medicalised' by irrigation treatment, they replied:

"Possibly yes, I don't know why that comparison as opposed to taking pills kind of for, you know, for years cos that's medicalising it too, but I suppose it is more the.. it is easier in some ways to kind of pop a pill, than it is to get all the kit out and kind of take the time and then, you know, be in the loo for that amount of time, but then I appreciate that there are going to be side effects and disadvantages to medication so it is certainly useful to try something that may not give them side effects." [C HV]

One further interesting aspect to this theme was that before starting treatment, some participants expressed a preference for one system or other. Some participants based this on their own conceptualisation of the effects of each system, and how they felt this would improve their symptoms;

"I remember thinking I hoped I was going to be allocated to the low-volume kind of condition, just because intuitively it feels like pumping a reduced amount of water would be kind of easier and better" [C HV]

"Just intuitively it doesn't feel kind of natural or normal to be pumping water up, you know… … So it kind of felt like actually it would be less comfortable, the kind of higher volume would be more uncomfortable than the lower volume" [C HV]

"I think I was happy to be honest, I don't know if it's [High-volume irrigation] *a better type of irrigation, but the way I was reading it I thought it would suit my symptoms better, so…" [D HV]*

A further participant based their preference on previous (negative) experiences with 'colonic irrigation' therapy;

"I think I was quite happy to do the low one… … I thought the higher one would be more like the colonic irrigation, more painful or more intense." [B LV]

"I just thought there'd be a lot more water and that it would be a lot higher pressure. When I did the colonic irrigation they would increase the pressure a lot until it was quite painful and then sort of let it go and it would pull everything out, so it doesn't feel like that, it just feels, Um, obviously there's a lot less water and it's just quite sort of relaxing really" [B LV]

"…it's been very straightforward, and just enough really. I have been doing it sort of three squirts each time just to feel that it was quite clean and well done, whereas maybe if I'd done the high volume one maybe I wouldn't need to do it so

many times. I don't know, obviously I've got nothing to compare with, but yeah, it's a lot different to the colonic irrigation that I'd experienced." [B LV]

The transition from the theoretical explanation given in clinic to regular home use was another aspect that participants described. One participant found the practical aspects of the procedure easier to master than they had expected, and learned rapidly how to use it at home:

"I thought it was a lot, a lot easier than when you talk about it… … I said I'd try it at home, I tried it at home, it was a piece of cake!

"The first trial was a bit messy on the floor like, with the water on but I tried it again and it was quite good but I was sitting this way, I'm right handed; I had the pump on the left hand side so I had to use me right hand and it's a bit awkward with [disability]…<mumbles>…It were great the second time."[A HV]

Other patients described positive aspects of using irrigation despite the fact that it was not especially effective for them:

"*Quite easy, yeah, once you get the hang of it. Yeah, it's quite straightforward and you know, you get all the, you know, the throw-away nozzles and it's all hygienic and clean and, you know, it's fine, yeah fine."[E LV]*

" I don't know if it's good about using the treatment in terms of positive benefits yet, but I think it's less bothersome that I first feared it might be. So there's a practice effect clearly, you get used to the routine, it's not as troublesome as it originally was." [C HV]

6.2.1.3 Theme 3: Attitudes towards, and experience of, using irrigation

Participants reported a broad range of attitudes and experiences with regard to using irrigation at home. Especially prominent aspects of this included fitting the treatment into their daily routine, and finding their own way of using it in order to maximise benefit. Elements of this theme that emerged included the importance of 'privacy' and 'routine', as well as overcoming some of the technical challenges of the procedure. One participant highlighted the differences between using the irrigation in the clinic setting and transferring that to their own home environment:

"It seemed a bit harder at home, thinking well, I haven't got this nice little sink and I haven't got the bed with the paper thing, and it was just, right, where do I get comfortable, what position do I need to be in, and, two or three times and you got used to your own routine." [D HV]

The concept of 'routine' was common to several participants, along with the logistics of setting up the device in the home. Nested within this was the importance of privacy and finding a quiet place to perform irrigation. One participant described their experience as follows:

"…some days I come round to doing it and think I can't really be bothered to go through all the setting up, but once I've decided right, I'm going to do it and I've locked myself in with my jug of water then it's easy to do; it's just the initial going in and setting it all up, but it takes seconds to do, so once I've got in the frame of mind that I've got some time to myself then it definitely helps me feel a lot better, makes me feel a lot healthier

"I think [privacy has] *been an issue in the past when at work when I was a teacher I felt that I could only go to the toilet at definite times, um, and even going back to school in the multiple toilet block you didn't want to go to the toilet and sort of pass anything for fear of the noise and smell and things like that, so I just became over the years able to hold it in. But now, with the children as well, they like to come into the toilet with me and it's obviously a bit of an issue of they would say things to people if I did anything, so I like to be completely on my own with the door locked, even in my own house, then I feel like mentally ready to try and pass something." [B LV]*

Other participants gave a clear picture of how they had incorporated the irrigation into their regular schedule:

"Doing it at the same time every day, I thought if I try and build it into sort of like shower time, on a night, right; 15 minutes before shower time this is what's going to happen and then sort of knowing there's going to be no disruptions, I know there's nobody going to knock on the door, everything's locked up so that helped, doing it at the same time every day" [D HV]

"*Fine, it's fine to fit in, it's easy enough it's just, you know, obviously you've got to be at home and everything and things need to be close by, and a bit of privacy and things like that, so. But it's fitted in fine, cos I've been quite housebound with what's been going on anyway, so I don't get out much at the moment, so..." [E LV]*

"…but I think it's less bothersome that I first feared it might be. So there's a practice effect clearly, you get used to the routine, it's not as troublesome as it originally was." [C HV]

Technical problems were encountered by some participants in the early stages of using the treatment. Two participants described feeling as if the issues they experienced were 'my fault' or down to 'stupidity' on their part, rather than due to inadequate training:

"A bit of technical issue with too much air in the tubes and I was inserting the air rather than the water which wasn't very pleasant but that's my fault for not setting it up properly so I wouldn't say there's anything negative to do with the treatment at all" [D HV]

"I encountered a kind of blip that was more my kind of stupidity just in the first few trials of it, in that I was turning the kind of device the wrong way round so rather than just go to the kind of, the, you know, the kind of white balloon, I was skipping round via the green so the balloon was deflating. I worked out that in a couple of days, so I suppose the procedure was well explained, I feel that I understand it and I'm kind of getting on with it really"[C HV]

Another participant described getting used to managing the device with a physical disability

"The first trial was a bit messy on the floor like, with the water on but I tried it again and it was quite good but I was sitting this way, I'm right handed; I had the

pump on the left hand side so I had to use me right hand and it's a bit awkward with me (disability)…<mumbles>…It were great the second time." [A HV]

One patient actually described the fact that they had to form a routine as having a therapeutic benefit in itself, as it caused them to focus on emptying their bowels more regularly. When asked what the best aspect of using treatment was, they replied:

"Probably the routine again, that it's given me something to focus on every day, that I need to give myself 10 minutes on my own and the toilet to actually try and do something about the issue." [B LV]

In addition to the practical aspects of using treatment, another commonly-expressed theme was the idea that it was still 'early days', and that they were hoping treatment would become more effective or better for them over time. This view was expressed most often by patients who had not found the treatment to be very effective up to that point, as one might expect, but also by those who had tried other therapies and found that they only brought short-term benefits.

"I think maybe in another month or so I'll be able to feel the benefits; at the moment I probably do feel a bit better, but I've gone through like trying different things and feeling better and feeling worse so at the moment it definitely feels like it's making some impact" [B LV]

"…it's only three weeks in… … I'm committed to kind of, you know, to keep trying" [C HV]

"I'm just happy to keep trying and hopefully see if we get some more positive results from this, cos it is early days" [D HV]

One further aspect of this theme was participants' willingness to try treatments, and the fact that they tolerated treatment well even if it was not as effective as they had hoped. This reflects the extremely negative impact that constipation symptoms may have on quality of life. One participant described their experiences of living with the condition:

"Well I suppose it's reflecting over almost a 30-year period, and it's just you become used to a kind of general level of misery, specifically about kind of, bowel habits, really. So travelling was difficult, you know, just the kind of normality or the regularity of being able to go and kind of empty your bowels the way everybody else did, just never happened for me, so there'd be that constant sense of having a full bowel, discomfort, you know, abdominal discomfort and not being sure kind of what to do about that." [C HV]

"I think that the initial treatment that I had was so, I know it sounds dramatic, but was so life-changing that I'm not sure I'm seeing a stepwise improvement from the irrigation if you see what I mean. Those early kind of periods of advice were wonderful, I can't praise them highly enough." [C HV]

Participants frequently compared and contrasted irrigation therapy with previous treatments, both in terms of the practical aspects of using irrigation and also in terms of effect. When asked about negative aspects of treatment, one participant replied:

"I think that it's the time that it takes to do it. I know you maybe think 15-20 minutes isn't a long time but I suppose you know, well, I could just pop a laxative in and in 30 seconds it might do a similar job, or a suppository doesn't take that time, I think it's just sort of setting it up and the time it takes, just trying to build it into your routine" [D HV]

Despite this, and the perceived lack of efficacy of the treatment, they would recommend it to other people, stating:

"I'd try anything… … You've got to try everything, cos what suits one person might not suit another, and if it just eases your symptoms a little bit it's doing something rather than being in pain and suffering. I'd certainly give it a go." [D HV]

Another patient found the experience of using irrigation superior to laxative use in terms of the practicalities, although the treatment was ineffective for her:

"…and I'd have been happy to continue it every day, the rest of my life if I had to, you know, rather than take laxatives" [E LV]

However, the experience of side effects were one negative aspect of using treatment described by several participants. The degree to which they were tolerated seemed to be related to the effectiveness or otherwise of treatment. One participant using high-volume irrigation experienced involuntary leakage of water between irrigations, something they described as a "potential deal-breaker", especially as the treatment had not brought them much benefit.

" I guess what I'm finding is that problem, that side effect that I'm having with the leaking, is quite a potential deal-breaker, that's not great. Also I guess I'm

not feeling that I'm getting a bowel-emptying yet from the process, I'm rarely passing stool, you know, I'm evacuating water but I'm not doing much more than that at this point. Again, that may change so I'm happy to persist to see". [C HV]

However another participant who described peri-anal discomfort found this much more manageable, and worth going through for the sake of the benefit they were getting from treatment.

"Um, probably just the slight pain, or the discomfort rather, on the first time that I use it. I try to use it three times each session, and the first time that the probe goes in it's always quite sore, so that's probably the worst bit that I don't look forward to."[B LV]

It was also interesting to note that one participant spoke more broadly about their experiences of participating in research in general:

"It's just that I think that it is really reassuring to know that, as I said before, that this is a focus of research, to know that it's not simply a condition that people don't talk about and you shouldn't mention, to know that something actively is happening." [C HV]

It therefore seems that, for this participant, the act of participating in research was, in a way, reassuring and beneficial. It is hard to know whether this had any additional therapeutic effect.

These themes illustrate the broad range of lived experiences described by chronic constipation patients during training and initial home use of trans-anal irrigation therapy. In particular, they demonstrate how the particular attitudes and pre-treatment experiences of the individual participant can have a significant impact on their experience.

6.3 STUDY SAMPLE 2: AFTER 6 MONTHS OF STUDY PARTICIPATION

Following on from the themes identified above, further face-to-face interviews were conducted after 6 months of study participation, in order to identify new themes specific to longer-term use of irrigation, or reasons for discontinuing therapy. This also provided an opportunity to re-visit and re-explore some of the themes from the previous interviews, in order to deepen and enrich the description of the participants' lived experiences. However, it should be noted that the delays in commencing study recruitment, combined with the fact that several patients either declined to be interviewed or were unable to travel to the hospital for an additional visit, meant that the pool of potential interviewees was smaller than had been hoped for initially. Therefore the heterogeneity of the study sample was limited, and there was a corresponding lack of depth to the range of experiences discussed. It can therefore be said that data saturation has not been reached at this stage. However, given that this study is nested within the much larger, multi-site CapaCiTY 02 trial, this data provides the first fully described into the phenomenon.

Of the participants who had been in the study for at least six months, three were willing and able to give consent for a further interview. Of these, one male participant and two females were interviewed. These participants had all been

interviewed at the 1-month time-point as well. Of these three, one was still using HV irrigation, one was still using LV, and the other had discontinued HV irrigation after less than three months. They were anonymised in the same way by being assigned a letter (A-C) and an irrigation system ('HV' for high volume and 'LV' for low volume). Additionally, patients were categorised as 'early discontinuation' (ED), or 'continuing use' (CU).

6.3.1 CODING AND THEME IDENTIFICATION

As for the previous interviews, transcripts were reviewed and significant words and statements were identified; these three interviews yielded 132 such statements. These were grouped together into 21 categories, and then into four broader 'themes', as follows: 'Treatment efficacy'; 'Practicalities of treatment use'; 'Impact of treatment on wider health and daily life'; 'Attitudes towards treatment'

6.3.1.1 Theme 1: Treatment efficacy

For all patients interviewed, their perceived treatment efficacy was seen as a very significant factor in determining whether they continued to use the treatment, and what effect it had on other aspects of their life. Of the three patients, two felt that they were still deriving benefit from irrigation after 6 months (one HV, one LV). The other patient had discontinued treatment after approximately six weeks of use. When asked about their reasons for stopping, they replied:

"I didn't find it was benefitting the symptoms I had; my main symptoms were the bloating , so it just didn't seem to help that so I didn't feel the need to carry on with it" [C HV ED]

They went on to elaborate that, while they had not found the treatment especially difficult or unpleasant to use (see theme 2 below), the lack of efficacy meant it was not worth persisting with treatment.

"…it didn't help with any of the symptoms that I had, so, and a lot of the substance I was passing just seemed to be watery, there was not a lot of colour in the water and things, which [irrigation nurse] said is quite normal anyway, but I just didn't feel it helped" [C HV ED]

"I just didn't want to feel like wasting anybody's time cos I know you're all busy and you've got other patients and I thought, well, if it's not helping me it might be beneficial for someone else to try it" [C HV ED]

The reference to their main symptom being the bloating was revealing, as it demonstrates that particular symptoms will be important to particular patients, and that this influences their experience of illness, and therefore informs their attitude towards therapy. Bloating was a significant symptom for another participant, but they were getting considerable relief from using the irrigation:

"I get a really bloated tummy, a really hard tummy, and I don't know if it's just in my mind or whether it's definitely working but when I use the irrigation system it definitely makes me feel a bit lighter, and able to sort of get rid of maybe the excess trapped wind that there is in there, in my tummy, so I like using it really" [B LV CU]

Another patient who had persisted with using high-volume irrigation described their main symptoms as incomplete evacuation and straining to pass small bowel motions, resulting in frequent trips to the toilet:

"I can go 5-6 times and not pass anything, and just maybe go, out of the 5-6 times go once, and just pass half a small finger worth of stool. And I'm wanting to go all the time, edgy, on my seat all the time" [A HV CU]

However, the perceived impact of the treatment for this particular patient was dramatic. They said it "worked…100%" and commented;

"so I use the water solution and I, it's there, you just do it straight away, use it, you go outside, walk around, clear; if you don't use it you're stuck indoors all day" [A HV CU]

Participants' perceptions of the mode of action of treatment, and how they felt it was working, was a further aspect to this theme. One participant commented that the sensation/perception of the water going in, and feeling it working, was a significant reason why they had persisted with the treatment. They felt that this gave the irrigation a clear advantage over some of the oral agents they had tried previously:

"I think it's the actual feeling of the water going in and the pressure, a bit like colonic irrigation that I've tried before, that makes you… it comes out naturally without having to do anything, yeah" [B LV CU]

This description of bowel motions as being more 'natural' with the irrigation was only described by one participant, but it was a theme that occurred several time during the interview:

"it's not like the products where it's making me want to go, it actually makes it come out with the water, so, um, I don't need to sort of worry about having to hold it in, it just, it comes naturally, so I definitely think this is better than the sachets and things like that that I've taken in the past" [B LV CU]

"I don't really need to push or do anything, I just go to the toilet, use it and it comes out and then after a minute or so I just leave. So, yeah, it's a different way of thinking" [B LV CU]

This perception can be contrasted with the feelings of another patient interviewed at one month (see section 6.2.1.2), who felt that the irrigation was 'mechanical' and having to use it reinforced their sense of things being abnormal.

Tied in with the theme of treatment efficacy is the effect of the passage of time. As detailed in section 6.2.1.3, several participants expressed the view that, after one month, it was still 'early days' and they hoped that the treatment would be more effective as time went on. Having interviewed participants after six months, diverse experiences of temporal aspects emerge. One participant [C] discontinued due to lack of perceived treatment effect as outlined previously. However, another participant felt that the treatment effectiveness had actually increased slightly over time:

"I think it's got better, um, I think it's helped more over the time but, um, I think I sort of sit and let it work for a longer period of time than I used to so I think it's more beneficial now, but as I say I definitely notice when I haven't used it for a couple of days." [B LV CU]

This idea of symptoms relapsing if therapy was discontinued was important to both participants who were continuing to use the treatment. Participant B describes above how they notice the difference after a few days of not using the treatment. They also describe a degree of anxiety about symptom relapse if they omit this treatment, and stated that this was an important factor in making the effort to use it:

"…I feel that I still need to do it and get in the routine of doing it cos sometimes I can go a couple of days without doing it properly, um, and yeah it's just got into a bit of a routine, I'm a bit scared that if I stop doing it then I'll just go back, go backwards." [B LV CU]

Additionally, there was an episode when ill health prevented them from using the irrigation for a period of time, leading to a relapse in symptoms;

"…I did stop for maybe a week or so, um, cos of the anxiety that I was suffering from and I did notice then that it seemed to be worse…" [B LV CU]

Another participant reported stopping the irrigation to see if the benefit was maintained, but found that they experienced significant symptom relapse:

"If I don't use it I could be on the toilet three quarters of an hour, and it's the size of your small finger, and then you finish, give up, walk downstairs, the feeling's there that you want to go again; so you go back upstairs, nothing.

"I tried doing without it [the irrigation] *and you can't do it" [A HV CU]*

The various aspects of this theme demonstrate the breadth of different experiences described by participants in this study, even though numbers are small. This highlights the highly individualised lived experiences seen amongst this patient group.

6.3.1.2 Theme 2: Practicalities of treatment use

Interviewing participants after a longer period of treatment use allowed for a focus on the practical aspects of treatment. At the one-month stage, participants described a '*practice effect*' (that is, a learning curve), and a process of getting used to using the treatment at home and fitting it into their daily routine. Amongst the two participants who continued with irrigation, this theme emerged again in a number of ways. One patient reflected on their initial difficulties that were quickly overcome, and gave a detailed description of the process of using the irrigation in relation to bodily position and use of the equipment;

"…over the weeks it was, it came, came to us, just, you know, quite easy to use, as long as you sit on the toilet, upright, relax, take your time, let it go, flush through your system, And it works really good" [A HV CU]

"…if you sit upright on the toilet, back straight, relax yourself, it just goes straight into the toilet, but if you lean forward you might dirty the wall behind you…

They also commented on how the initial experience of being trained by the irrigation nurse was relevant to their own experiences of using it independently, and how they had adapted this technique to suit them;

"I was… what <irrigation nurse> says… showed us how to use it, I've used it that way. You improve slightly; you do better the next time you do it. You hang it up on… you know, your bag up. You improve what you're doing and you just… I get up on a morning, get out me bag, fill up with water, hang it up, straight away ok." [A HV CU]

Another participant described the process of incorporating irrigation into their daily routine, but emphasised the difficulties they were having fitting this in around their family commitments. Nonetheless, because of the perceived benefits they were getting, this was something that they were prepared to make an effort to do:

"…sometimes it's quite restrictive, in that it's hard to fit it into my daily life. Sometimes I get into a routine with the children and sort of forget about doing it. But I do notice if I haven't done it for a couple of days that I get a really bloated tummy, a really hard tummy…

"…if I haven't used it for a couple of days it's quite easy to get into a routine of just ignoring it again.

"It's not always easy for me to do it first thing in the morning, um, but I try and do it around tea time, and that's quite a good time for me to fit it in, um, and I definitely feel cleaner and more empty when I've used it." [B LV CU]

The participant who discontinued treatment described a similar process of overcoming minor technical problems and incorporating it into a routine, which they achieved without too many problems; they said that, had the treatment been effective, they would have happily continued to use it.

"it was absolutely fine, it was easy to set up, it was all explained well by [irrigation nurse] and yourself, and [research nurse] had some input. Um, once I got used to it, it was relatively easy and didn't take much time up

"…after a couple of times, a little bit technical issues to start with, where too much water, not enough, too much air in the system, but once you got a couple of days out of the way it was fairly easy."[C HV ED]

When asked how easy it had been to fit the irrigation into their daily routine, this participant replied:

"Oh, really easy, yeah. I tended to stick to it the same time every night, so it was shower time; do your treatment, go and have a shower, so it was just 10 minutes out yer day" [C HV ED]

Only one of the participants experienced significant adverse events of treatment, as they developed anal pain which persisted on most occasions that they used the treatment despite taking measures to prevent this:

"Just sometimes it's sore, it's usually sore on the first time that I use it, particularly if it's been a couple of days since I've used it, even if I sort of, um, wet the end of it to lubricate it it's still quite sore when I put it inside, um, so that sort of sometimes puts me off wanting to use it but after I've used it the once, then

obviously when I use it the second time then it's ok. But I'd say generally most of the time on the first time that I've used it, it's been quite sore" [B LV CU]

Although this was clearly an unsatisfactory aspect of the treatment, when asked if this was something they were prepared to accept if the benefits of therapy were maintained, they replied:

"Well it would be nice to be different but yeah, I'm willing to accept it because I think the benefits outweigh that problem. At the beginning of the trial when the nurse did some sort of invasive investigations it was quite sore when she did that so I don't know if there's an issue that needs to be resolved, I thought it was something that would just go away with time but it's continued, or whether it's just part and parcel of this treatment that I'm following, but it's definitely worth, it's manageable. It's not terrible, the pain, it's just uncomfortable" [B LV CU]

The participants held contrasting opinions on how irrigation compared with drug treatments or other therapies. These attitudes seemed to tie in strongly with other aspects of the participants' experience of illness and what it meant to them.

In contrast, another participant described how they would rather use a tablet if it gave them the same effect, however no medications had worked before trying the irrigation so they were happy to continue.

"If there was a tablet, a medical tablet what you could give and it gets rid of that 'you could go to the toilet all the time' I would take it but at the moment there's none. At the moment I'm on the water irrigation and it helps me 100%, so if I stop on forever I'll stop on forever." [A HV CU]

6.3.1.3 Theme 3: impact of treatment on wider health and daily life

This theme ties in strongly with treatment efficacy; however, participants made several statements about the impact trans-anal irrigation has had on their wider health that shed some light on the complex nature and impact of their constipation symptoms, and illustrate how a particular therapy can have effects beyond simply improving these. Therefore these particular elements of the participants' experience are discussed here.

One participant gave a clear account of how the constipation symptoms were affecting them, causing them to not be able to go out when they wanted due to a constant feeling of incomplete evacuation and straining to pass small bowel motions. These symptoms were made significantly better by using the irrigation, and the participant was extremely happy about this. This is how they described the difference:

"well If I don't use it, I'm wanting to go to the toilet all day. I can go 5-6 times and not pass anything, and just maybe go, out of the 5-6 times go once, and just pass half a small finger worth of stool. And I'm wanting to go all the time, edgy, on my seat all the time, so I use the water solution and I, it's there, you just do it straight away, use it, you go outside, walk around, clear; if you don't use it you're stuck indoors all day." [A HV CU]

"Before I was using it I wasn't, I wasn't going out anywhere. I was staying in, watching what I was eating, trying to eat wholemeal bread, things what make you go to the toilet, and it didn't work. I was stuck in the house, couldn't go anywhere…

Cancelled holidays, cancelled a holiday to Mallorca for 2 weeks, full board; didn't go. Me wife went, me daughters went, I stopped at home." [A HV CU]

This had clearly made a very significant difference to their quality of life. One specific example of this (from the same participant) was as follows:

"See I like to go out with the dog and I'm out maybe three hours, four hours with the dog, walking her. I've got nowhere to go to the toilet if I'm out with the dog, if I don't use it. I've got the feeling of wanting to go to the toilet and I want to take her out and run straight back home to go to the toilet and when I get back home, can't do anything.

"So when I use the irrigation once a day in the morning, I'll be out all day." [A HV CU]

These examples illustrate the broader benefits that effective therapy has brought to this particular individual. They show in a vivid way how restrictive chronic constipation can be.

For another participant, one very significant aspect of the treatment was the fact that it gave them time each day to try and have a bowel motion, whereas previously this participant had been in the habit of trying to 'hold on' and 'turn off' the feeling of needing to go to the toilet, which they felt had been exacerbating their symptoms. This idea of habit-forming and habit-breaking came across very strongly in the interview:

"for the whole of my life really I've been able to just sort of squeeze it in and forget about it, turn my brain off, so that I end up with a really big tummy, I can go

for maybe 2 weeks without going to the toilet, but it's quite easy for me to turn off the feelings of needing to go…" [B LV CU]

They went on to describe how they would slip back into old habits if they omitted to use the irrigation:

"if I don't get into the routine of using the irrigation system it goes quite quickly back into the old routine, so you just have to try to get into the way of doing it a specific time every day, when I've got a bit of time away from the children, and I can be without interruption." [B LV CU]

This participant gave a vivid and clear insight into the thought process behind the bad habits they had developed over the years, and how doing the irrigation had caused them to think differently about their toileting habits:

"…it's a weird feeling, it's almost like an achievement that I feel that it's, er… I don't like it at the time, it sort of brings a few tears to my eyes sometimes when I sort of hold it in and it can take like a minute or two for the feeling to pass but then once it's gone and I feel like 'oh, I'm back to, I'll just get back on with my life'. So I don't know, I understand when I'm saying it out loud that it's not a good thing to do, um, that it seems a strange thing to do but I think I've just always done it since I was a child, so, um, I think when I was a child I didn't want to stop playing or I didn't want to stop doing what I was doing, so I didn't like going to the toilet for a long period of time, so I'd just hold it in and after a minute or two I'd just get back on with it, so I've always done that. But with this trial, the irrigation system, um, I don't really need to

push or do anything, I just go to the toilet, use it and it comes out and then after a minute or so I just leave. So, yeah, it's a different way of thinking" [B LV CU]

Looking beyond constipation and bowel function, this participant also talked about how using the irrigation had brought about positive changes in other areas of their life. For example, they described the feeling of excess bloating and having a hard abdomen, and wearing baggier clothes to conceal that. This had an adverse impact on how the participant viewed themselves, and on body image:

"…it makes me feel like I'm a lot bigger than I am

"But that's always been the case, so I like to wear sort of clothes that are a bit baggier" [B LV CU]

They felt that the irrigation treatment had improved things in this area, stating

"Yeah, it definitely does [help], yeah. It helps a bit".

They also reflected on their long-term health, and reported feeling that the constipation would have an adverse effect on this, especially in view of the fact that a family member had recently been diagnosed with a serious bowel condition. They commented:

"I was concerned at the beginning it would have an adverse long-term effect on my health, so I feel that when I'm using it then at least I'm making some kind of positive effort to, to become more healthy"

"…the trial's gone hand in hand with the anxiety I've suffered since Christmas so, um, yeah, with the anxiety sort of settling down then I've started exercising more

and that, that helps as well. But yeah, so I think they probably go hand in hand, that the lighter I feel the more I want to exercise, the more energy I have." [B LV CU]

These statements illustrate some of the ways in which bowel symptoms, and effective treatment for these, can have a profound effect on many aspects of patients' quality of life.

6.3.1.4 Theme 4: Attitudes towards treatment

This theme uncovered participants' views on the treatment, irrespective of whether or not it worked. Key aspects of this theme included participants' willingness to try new treatments (due to the high symptom burden and lack of success of previous therapies), and whether they would recommend this therapy to others.

While a key reason given for discontinuing therapy was perceived lack of efficacy, the participant in this study who discontinued treatment after a short time nonetheless expressed positive opinions about it:

"Oh, I would try anything, so I'm open to trying any treatment, so it didn't panic me or concern me when they mentioned irrigation

"…Nothing nasty or awful about it. People might think 'ooh, it's not clean or hygienic' and you read different things, but no, I didn't have any concerns

"I'm quite happy to have tried it, and just unfortunately it didn't work!" [C HV ED]

When asked if they would recommend trans-anal irrigation therapy to someone with the same condition, they replied:

"I would, I would say try anything, personally. If you don't try it you don't know it's not suitable or if it is suitable, everybody's different

"It's not unpleasant; it's nothing to be embarrassed about. You fit it into your daily routine easily, it's quick to use, it's discrete; the packaging comes nobody knows what you're getting delivered, and if it works just try it, and if it is working keep going." [C HV ED]

Participants who had derived benefit from therapy also made very positive statements about it. One participant stated:

"I'm really satisfied with it; I'd recommend it to anybody. I'd probably go round the hospital and show people how to use it!" [A HV CU]

When asked about how they would feel if they had to continue using irrigation long-term, this participant replied "[I'm] happy to carry on forever… …if it helped us, yes".

Another participant had experienced side effects that they clearly found unpleasant. However, they still felt they were deriving sufficient benefit from using the irrigation, stating:

"Well it would be nice to be different but yeah, I'm willing to accept it [the side effects] *because I think the benefits outweigh that problem… …I thought it was something that would just go away with time but it's continued, or whether it's just part and parcel of this treatment that I'm following, but it's definitely worth, it's manageable. It's not terrible, the pain, it's just uncomfortable." [B LV CU]*

When asked whether they would recommend the treatment they responded *"yeah, definitely, I think it gives you peace of mind".*

This provides some idea of the spectrum of different perspectives on the therapy seen in a relatively small study population. Due to the small number of participants and the lack of representation from some key groups within the study (for example, those who switched therapy and those who discontinued later), it cannot be said that data saturation has been reached for the six-month time point. However, the themes that have emerged are highly instructive, and add to our understanding of the experiences of patients using trans-anal irrigation therapy for chronic constipation.

6.4 DISCUSSION: THE ESSENCE OF THE LIVED EXPERIENCES OF STUDY PARTCIPANTS

This qualitative enquiry has identified a range of themes and statements from a variety of participants that can inform our understanding of the lived experience of patients who begin using trans-anal irrigation therapy as a treatment for chronic constipation. It has already been suggested in the literature that patients with functional and/or other defecatory disorders have had many negative experiences of healthcare, including unsatisfactory or ineffective treatment, difficulties in accessing healthcare and pejorative attitudes towards them from health professionals (92)(93). A previous qualitative study into rectal irrigation had found a range of pre- and post- treatment experiences ranging from finding the treatment burdensome, to finding it to be life-changing(93).

To understand the participants' experiences of irrigation training and home use, it is necessary to set these relatively recent short-term experiences within the much more complex long-term context of the participants' experiences of living with chronic constipation. Talking to these participants, it is evident that many of them have had strongly negative experiences of their condition over the long-term. Several spoke about feeling 'not normal' or embarrassed by their condition, as well as being severely limited by it in terms of what activities they feel able to undertake. Furthermore, chronic constipation is not precisely defined and represents a cluster of symptoms; the most significant symptom or symptoms described by a particular individual varies significantly between participants. Understanding these broader aspects is essential in trying to contextualise a particular individual's experiences with irrigation.

As regards the irrigation training itself, many interviewees expressed appreciation for the irrigation nurses, commenting especially on feeling well-supported and feeling at ease in the clinic setting, despite many of them feeling apprehensive beforehand. This aspect of clinical care appears to be especially important in a patient group who have sometimes had negative experiences of healthcare (92)(38). However, it should be noted that the interviews were conducted by a member of the clinical team and that this may have resulted in participants being unwilling (consciously or unconsciously) to be critical of the care they received. This was one potential limitation of this study. It is also possible that patients felt able to be more frank and willing to talk honestly about private bodily functions more easily to a researcher with direct clinical knowledge of the disease. Further work is necessary to

establish a more complete picture of this element of the patient experience; interviews away from the clinical environment, and conducted by interviewers with little direct involvement in participants' clinical care, may give a more complete description.

Following on from the theme of anxiety and embarrassment, it is interesting to note that participants expressed a range of differing opinions about aspects of the training itself, in particular they were divided on whether carrying out an irrigation in the clinic setting was beneficial. Some did not want to do this as it made them feel ill at ease, either due to feeling of embarrassment about their condition, or because they were not comfortable being shown by a nurse of the opposite sex. This serves to highlight the importance of cultivating good relationships with individual patients, and maintaining sufficient flexibility in the training to tailor this to the needs of the individual. In addition, it should be recognised that patients have a number of pre-conceived ideas and attitudes towards trans-anal irrigation therapy and what this involves. This study has shown that these may be based either on media sources, the study patient information sheet, or on their own experiences of undergoing 'colonic irrigation' privately. These preconceptions may have a strong effect on how patients feel about starting therapy. For instance, in this study one participant spoke of their disappointment in having to do something 'mechanical' in order to treat their constipation. Others spoke about having a preference for one system or the other based on what they had read about each one, and how this related to their previous experiences or preconceptions about how the treatment would work for their particular symptoms.

The next stage in the patients' experience concerned adapting the training to their own home circumstances and daily routine. There was a commonly-described process of learning to use the irrigation, with several participants describing initial technical difficulties and practical problems, but it appeared these were swiftly overcome. The statements made about this process offer a clear insight into what it is like for people to use irrigation at home. Several participants also emphasised the importance of finding a private and quiet place in order to carry out the irrigation. One participant was actually glad to have the irrigation as they felt it gave them focus and made them take the time to go to the toilet, while previously they were in the habit of holding stool in and thereby exacerbating their symptoms.

Once the treatment was an established part of their daily routine, the reported experiences of the participants then began to differ markedly, largely based on how effective the treatment was perceived to be. Effectiveness of treatment emerged as a very significant theme at both time points, and participants' perception of how well (or otherwise) the irrigation therapy was working for their particular illness had a very significant bearing on their attitude towards it, and in particular whether they persisted with treatment.

Participants for whom treatment was effective described a sense of freedom and of re-gaining control, of being able to break bad habits, and of being able to go outdoors for longer without the same degree of anxiety they were experiencing previously. One participant, for whom treatment was very effective, described a sense of 'cleanness' after irrigation that they had not experienced with other treatments.

On the other hand, if the treatment was not effective then participants did not describe any improvement in their quality of life, and their experiences were nothing like as positive. Interestingly, these participants described few negative aspects to the therapy besides the lack of efficacy. They were in agreement that if the treatment worked, they would happily carry on. One did describe one particular side effect (post defecation leakage) as a potential 'deal-breaker', and also commented on the time it takes to perform irrigation as being a disadvantage, however these issues seemed to be much less important in comparison to the symptoms experienced.

In the longer term, continuing use of irrigation (if successfully treating symptoms) seemed to bring about more wide-raging health benefits, and to improve the participants' quality of life in a more general sense. Participants described reduced anxiety, increased social participation, improved body image and an increased sense of control and ownership over their own health. This demonstrated that effective treatment can have wide-ranging health benefit for the individual. These effects are almost certainly not specific to trans-anal irrigation, and indeed some participants expressed the opinion that they would rather take a tablet than do the irrigation, if it had the same effect. One participant compared the irrigation (which had not been especially effective at that stage) with an oral treatment they had tried initially (prucalopride), which had a 'life-changing' effect on their symptoms. Others, however, reported that they preferred to use the irrigation and that it suited them better than laxatives.

In conclusion, it can be stated that understanding the experiences of patients initiating trans-anal irrigation therapy depends on placing the treatment within the context of a chronic condition for which they may have undergone numerous other treatments with varying degrees of success, and which can have a profound impact on many aspects of their lives. The relationship between patient and irrigation nurse is of vital importance and the diversity of patients' pre-irrigation experiences, combined with a variety of different attitudes to the proposed treatment, means that a flexible and patient-centred approach to training is necessary.

The implications of this for on-going clinical practice and further research, as well as how these qualitative results relate to the quantitative arm of the study, will be discussed in the following chapter.

CHAPTER 7: DISCUSSION AND CONCLUSIONS

7.1 INTRODUCTION

Data presented in this thesis represent interim results from a single centre running within the Chronic Constipation Treatment Pathway (CapaCiTY) 02 trial. The fact that this trial centre (University Hospital of North Durham) had commenced recruitment earlier than any other site and had recruited a far larger number of participants than other centres at the time of writing means that, although the study was not designed as a feasibility study from the outset, it is a worthwhile exercise to present results in this way in order to inform ongoing conduct of the trial nationally. This feasibility study explores pragmatic, experiential and scientific aspects of running the CapaCiTY 02 study as per protocol at a single study centre, in order to identify potential challenges and to explore the appropriateness of the study outcome framework and follow-up schedule. Although the numbers recruited at this stage are too small to draw definitive conclusions regarding the comparative efficacy of each system, and the role of rectal irrigation therapy in treating functional constipation, this preliminary analysis of quantitative data, along with the qualitative study arm, provides valuable insights into the practicalities of running the study, and the feasibility of the recruitment targets and follow-up schedule. Findings have the potential to inform the successful conduct of a large publically funded trial, as well as future studies in this population.

In the following chapter, the main study findings will be discussed and their implications explored. Implications for further research, as well as an appraisal of what could have been done differently, will also be included.

7.2 SUMMARY OF MAIN FINDINGS

7.2.1 Current evidence for trans-anal irrigation

The systematic review and meta-analysis (see chapter 2) assessed the quality of current evidence for the use of trans-anal irrigation to treat chronic constipation. High quality trial evidence for this treatment is lacking, with all seven studies included in the analysis affected by methodological flaws and moderate-to-serious risk of bias. A fixed-effects meta-analysis reported a positive response to treatment rate of 50.4%, although there was evidence of considerable heterogeneity between studies. It can therefore be stated that, while there is some evidence that this treatment can be of benefit to patients with chronic constipation, there is a clear need for better quality randomised controlled trial evidence to establish a firm evidence base for its use.

7.2.2 Study feasibility

The CapaCiTY 02 study is ambitious in its scope and contains substantial complexities. There are no other randomized controlled trials of trans-anal irrigation therapy in functional constipation, and therefore it is important that this research is completed, in order to add to the (currently relatively weak) evidence base for its use. Many aspects of the trial were evaluated in order to determine whether the trial design was feasible, and whether it was appropriate for achieving the stated primary outcome of the CapaCiTY 02 trial (that is, to assess comparative effectiveness of high volume and low volume trans-anal irrigation therapy in patients

with functional constipation). In the first instance, the recruitment and retention rates were assessed to evaluate whether the study can reasonably be expected to recruit appropriate numbers to provide valid conclusions, and whether this can be achieved within the stated timeframe. In addition, quantitative data from the Durham site have been analysed with a view to evaluating the mean reduction in PAC-QOL between systems, along with the standard deviation, to further assess the appropriateness of the sample size calculation. The completeness of data collection, as well as interim survival analysis and adverse event recording, also form part of this feasibility analysis.

7.2.3 Patient recruitment and retention

Over the course of the study period, the initial target of one patient per month was exceeded at the Durham site. However, recruitment did not commence until later than originally planned due to delays in the protocol development and ethical approval process. This meant that the new recruitment target has been revised to two patients per site per month. For the period October 2015 – July 2016, the mean recruitment rate at the Durham site was 1.9, suggesting that this is an achievable goal. However, it should be noted that many other sites have experienced very significant delays in study commencement, and that recruitment overall has been well below target estimations. This is illustrated in Chapter 5, figure 1 and figure 2. This low recruitment rate nationally led to study sites being contacted to participate in a teleconference in order to identify barriers to recruitment and to develop strategies to overcome these. These were conducted on 9th and 10th August 2016

and involved five of the study sites recruiting (out of six sites open to recruitment at the time). Several reasons for low recruitment were identified, mainly the result of variation in local practice (making the protocol difficult to implement), as well as service pressures and the pressure on research teams to conduct more than one study in the CapaCiTY programme. This highlights the difficulties in implementing multi-site studies, and even though attempts were made before study commencement to ensure sufficient flexibility in the proposed study design, problems were encountered. One notable example was a site where Qufora-Mini irrigation was used very frequently as part of their biofeedback regimen, thereby excluding these patients from participating in the research. Another centre's standard practice was to train patients to use irrigation in the community rather than in the hospital; as the ethics approval for CapaCiTY 02 does not cover community working (other than for qualitative interviews), this made conducting the study at this site difficult. This illustrates the importance of thorough and complete feasibility work at the pre-study stage at each proposed site.

Regarding retention of participants, as of 18th August 2016, two of the 19 participants recruited to the study at UHND have withdrawn. One of these did so after the three-month primary outcome data collection, the other within two weeks of starting irrigation. No reason was given for these two elective withdrawals. This represents a drop-out rate of 10.5%. The sample size calculation incorporated a loss to follow up rate of 10% over the course of the study. This observed rate is therefore likely to be acceptable, however the small numbers of participants recruited so far

means it is difficult to give a reliable estimate of the likely loss to follow up at this stage. The qualitative work gives clues as to the potential reasons for withdrawal but further work is needed to fully understand the patient experience in this regard.

7.2.4 Appropriateness of the outcome framework and completeness of data collection

As previously described, the primary study outcome was assessed using the Patient Assessment of Constipation – Quality of Life (PAC-QOL) questionnaire(76), which is a validated outcome measure and is extensively used in the medical literature. Its purpose is to assess the impact of constipation symptoms on quality of life. Each item in the 28-item questionnaire is scored 0-4 by the patient, and the total added up to give a score out of a maximum of 112. This is then converted into a score of between 0 (no effect on quality of life) and 4 (very severe impact on quality of life) by dividing the total score by the number of completed answers (ideally 28). Therefore, if answers are missing or invalid, it is possible to allow for this in the score by dividing by the number of completed answers only (not by 28 irrespective of completeness).

In this study, the great majority of PAC-QOL questionnaires were completed fully (79% at baseline, 80% at 1 month, 91% at three months). The practice of checking for missing answers (introduced following clarification from the chief investigator based upon experiences conducting an earlier trial) has further helped to ensure that

this crucial outcome is completed appropriately. This suggests it is an appropriate and achievable outcome measure to use. Additionally, the PAC-QOL scored highly for ease of use and relevance during the pre-study constipation research advisory group meeting.

The CapaCiTY 02 study outcome framework is designed to be standardized across the three studies that constitute the CapaCiTY programme. In addition to the primary outcome (comparison of reduction in PAC-QOL between the systems), there are a large number of secondary study outcomes for which data is being collected. These are outlined in detail in chapter 3, sections 3.3.2 and 3.8. This has led to a fairly high burden of measurement for study participants in the form of questionnaires at each study visit, as well as diaries and journals to be completed throughout the study. This feasibility study has identified that, although the questionnaires are completed on a majority of occasions (see Chapter 5, table 3), the patient diaries (completed two weeks before visits 2, 4, 5 and 6) were much less well completed, with less than half of diaries completed (with no missing answers) at baseline and three months. At baseline, 21% of diaries were omitted altogether, and this rose to 36% at three months. The measures within the protocol to improve diary completion (i.e. a telephone call to remind patients, or an email reminder via REDCAP) proved unreliable; participants were often not able to answer the telephone, and also finding the time to contact patients proved a logistical problem for the research team. Furthermore, the REDCAP reminder email would often be delivered to participants' 'junk' email folder and therefore not be completed.

Currently, discussions are in progress with the trial sponsors as regards improving the reliability of the online REDCAP data entry system. If this works efficiently, it may well lead to improvement in the proportion of diaries being correctly completed.

Despite high levels of engagement in this highly committed population, the high levels of missing data suggest that the burden on patients is unsustainable. This is a key finding with implications for both the Capacity study and future studies in this population.

7.2.5 Primary trial outcome: Mean reduction in PAC-QOL

As previously described, the small numbers included in this feasibility analysis significantly limits the extent to which the primary outcome results can be relied upon to give a clear picture of what the overall trial result will be. The purpose of this analysis, therefore, is to provide descriptive analysis only, including an estimate of standard deviation for the purpose of evaluating the appropriateness of the sample size calculation. Overall, the mean PAC-QOL for the whole cohort did fall, from 1.95 at baseline to 1.35 at 1 month, then it increased slightly to 1.56 after 3 months (a net reduction of 0.39, SD 0.44). This initial decline followed by a sharp increase is very likely a product of the small numbers included; one HV participant recorded a very significant drop in PAC-QOL at 1 month followed by a rise at 3 months. As there were only six HV participants in total, this (potentially anomalous) result at 1 month will skew the mean value for the HV group and the whole cohort. It is interesting to note that the LV group demonstrated a mean reduction in PAC-QOL

from 2.12 at baseline to 1.73 at 1 month, but this was maintained at 3 months (PAC-QOL 1.76, a reduction of 0.36 SD 0.54). The mean reduction at three months was very similar between groups (for HV, it was 0.41 (SD 0.39) after 3 months, a difference of 0.04 in favour of HV). This tiny difference, if reproduced across the whole study, would not be clinically significant.

The potential for single outliers to affect results from the whole cohort will be greatly reduced for the study as a whole due to the large numbers to be included (150 participants in each group). The fact that the calculated standard deviations for each system and for the cohort overall are less than 1 (the estimated SD used in the power calculation) suggests that the sample size is sufficient for detecting a true difference between the systems if such a difference exists.

One interesting and potentially relevant element of these initial study results is the comparison between quantitative outcomes (PAC-QOL) and the statements reported by the same patients during their qualitative interviews. This allows a degree of triangulation of study findings, which could help inform understanding of the significance of the results. For example, one patient interviewed after 1 month and after 6 months reported very significant improvements in quality of life compared to before starting irrigation. This is reflected to an extent in his PAC-QOL scores, which were 2.28 at baseline and 1.04 after 6 months (a significant reduction of 1.24). However, his 1-month and 3-month scores were 0.57 and 2.04 respectively, meaning

the 3-month primary outcome reduction is only 0.24. Reasons for this erratic reporting are not immediately apparent. The participant's baseline 1-month PAC-QOL questionnaires do contain missing answers, but this is taken into account by dividing the total score by the number of completed answers, as outlined above, and is therefore unlikely to be sufficient to explain this. Furthermore, another participant reported significant improvements in their symptoms during their interview, and expressed satisfaction with the treatment, but their PAC-QOL score did not reduce (in fact there was an increase from 1.18 to 1.57 over the 3 months).

These two examples illustrate how a patient's perception of treatment success, or the degree of that success, can be highly subjective. This illustrates that any single quantitative measure of efficacy must necessarily be a compromise that cannot, of itself, provide a complete picture of how well a treatment is working. However, over the course of a large randomized study a more reliable picture should emerge which will allow valid conclusions to be drawn both as regards comparative efficacy, and regarding effectiveness of the treatment as a whole. This comparison also illustrates the value of combining qualitative and quantitative methodologies, and the extent to which they can combine to provide a fuller and more comprehensive illustration of the effectiveness of a treatment.

7.2.6 Safety reporting and adverse events

The mechanism for tracking and recording adverse events (i.e. participants recording these in the irrigation journal, then transferring this information onto the CRF at

each study visit) worked well, and the prospective tracking of adverse events is an important secondary outcome of the CapaCiTY 02 trial.

Initial experience of running this study has shown that, while minor adverse events are very common (occurring in 73% of participants in this study), no patients have come to significant harm as a result of participation in the trial. This is consistent with published studies, with one study reporting an adverse event rate of 74 %(50) (see Chapter 2: Systematic review). There have been two serious adverse events in the study so far, but neither was related to the irrigation treatment. Therefore this feasibility study has not highlighted any patient safety concerns as regards trial participation, and reported AE rates are consistent with published literature on the subject. The limited data on AEs currently in the published literature will be strengthened by the results of the full CapaCiTY 02 study once these are known.

7.2.7 Patient experience

In addition to the qualitative elements to the study outlined above, the qualitative work conducted with trial participants shed some light on many aspects of the patients' experience, both of training and home use of trans-anal irrigation, and of participation in a research study.

The nature of the essence of the lived experience of participants undergoing trans-anal irrigation therapy for chronic constipation is described in detail in Chapter 6, section 6.4. Key components of that experience concern the individual's pre-treatment experiences of living with constipation, as well as their previous experiences with other therapies, and of healthcare utilization more generally. This may explain the attitude of an individual when confronted with the prospect of starting to use irrigation. Key themes such as anxiety, embarrassment, and disappointment all emerged through semi-structured one-on-one interviews. This is important to recognise, as anxiety about investigations or treatment options could potentially be a barrier for some patients preventing them from starting potentially beneficial treatment. The key to overcoming this seems to be the relationship with the irrigation nurses, about whom most participants spoke very highly. It appears as though support from the irrigation nurses, both at the initial training session and afterwards, gave participants the confidence and reassurance to try the treatment. It is possible to suggest that irrigation nurses should be more closely involved in the recruitment process for this and future trials.

Within this small study cohort, five participants have so far discontinued treatment. One of these withdrew from the study without giving clear reasons. The other four all cited problems with side effects and/or ongoing severe symptoms of constipation as their reasons for stopping treatment. The qualitative research seems to indicate that efficacy (or lack thereof) is a more significant factor in whether patients discontinue therapy than the presence of side effects. One interviewee, who had

continued to use low-volume irrigation, described persistent peri-anal discomfort that was clearly an unsatisfactory element of the treatment. However, they went on to describe how they were willing to put up with this side effect because of the benefits they were getting from the treatment. Conversely, the interviewee who had discontinued therapy did not describe any significant adverse events, and said they would be happy to have carried on with the treatment if it had been effective.

Another interesting factor to emerge from the interviews was how patients described different symptoms as being the most troublesome. Some described abdominal pain and bloating as being their most problematic symptom; for others, it was a sensation of incomplete evacuation and difficulty passing stool. This demonstrates that members of this patient group have a complex and poorly-understood illness which is very heterogeneous in nature. This lends support to the decision to use a quality of life measure as the primary outcome, rather than focusing on one particular symptom. It also supports the collection of a diverse range of outcome data (including symptomatic data, psychological profiling and radio-physiological investigations) in order to build up as complete a picture as possible of how effective the treatment is, and in whom it is most effective.

7.3 SUMMARY OF IMPLICATIONS OF THE STUDY FINDINGS

This study has shown that the CapaCiTY 02 study is, in principle, feasible and achievable within the study timeframe. This is demonstrated by the adequate

recruitment rate at the Durham site, combined with adequate patient retention and sufficient completeness of primary outcome recording. However, there are some causes for concern, notably the overall poor recruitment rate across all sites and the delays experienced in commencing recruitment, with several sites yet to open. As detailed above (section 7.2.1.1), there has been active engagement with recruiting sites throughout the trial to date, aiming to identify and rectify barriers to recruitment.

A further problem identified as a result of this study is the fact that the Patient Diary is frequently omitted, or returned incomplete. It appears that the safeguards in the protocol aimed at preventing this (telephone call or reminder email 2 weeks in advance) have not been successful in overcoming this so far. If the completion rate for diaries remains low throughout the study then it is questionable whether valid conclusions could be drawn from any analysis of this data.

Nonetheless, this feasibility study does provide an important proof of concept and has not highlighted any significant safety concerns. The combination of quantitative and qualitative data has enabled diverse aspects of the patients' experience to be described, and this sheds light on important elements of patient care that are not explored by quantitative data alone. For example, the qualitative interviews highlighted some important aspects of the irrigation training, mainly centering around the relationship between the irrigation nurse and the patient. Participants gave conflicting views about some elements of the training, notably the option of performing the first irrigation in the hospital with the irrigation nurse available for

advice. Some participants found this very helpful whereas others found it uncomfortable or embarrassing (for example, being shy about being shown to use irrigation by a nurse of the opposite sex). This highlights the importance of flexibility and sensitivity in the irrigation training regimen, and these are clearly important factors to consider when developing this type of service. The fact that patients were influenced by pre-conceived views about irrigation gleaned from the media and other sources is of particular note and should be borne in mind when preparing patient information sheets and recruitment information.

7.4 CONTEXT OF THE STUDY FINDINGS

As previously described in Chapter 1, 'constipation' is a very common symptom among adults and children globally. 'Chronic' constipation, where symptoms have been present for 6 months or more, has an estimated global pooled prevalence of 14%(1). However, prevalence can vary significantly depending on the definition used(4). This is clearly a very heterogeneous condition, with no clear unifying pathophysiology to explain the symptoms described. Wide variations are seen between patients in terms of symptoms described and results of investigations(8).

Trans-anal irrigation therapy has become widely available as a treatment for chronic idiopathic constipation in the UK, although evidence for its effectiveness in this condition is weak, as outlined in Chapter 2. The meta-analysis performed as part of this thesis found a pooled response rate of 51% (random effects model), although the studies were heterogeneous and all were at moderate to severe risk of bias. All

studies were in patients using high-volume irrigation; the Qufora-Mini system has been the subject of one trial(68) assessing its effectiveness for patients with passive incontinence and evacuatory dysfunction. This reported improvement in symptoms in approximately two thirds of the 50 patients included, however the authors did not differentiate between the incontinence patients and those with evacuatory dysfunction.

There have been no prospective, randomized trials evaluating the role of irrigation in functional constipation. Furthermore, it is not known whether it is a better treatment for patients with particular symptom profiles or radiophysiological parameters.

The best current evidence suggests that, while side effects are common (see Chapter 2), these are minor and self-limiting. The reported rate of bowel perforation (the only serious complication reported in association with this therapy) is very low (2 per 100,000 irrigations in one study(58)).

7.5 LIMITATIONS OF THE STUDY

The CapaCiTY 02 study represents the first attempt made to conduct a large-scale randomized trial of trans-anal irrigation therapy. This has presented a series of challenges, both from a trial design perspective and in practical terms. This feasibility

study, as previously described, aims to identify and resolve potential pitfalls and to establish whether the stated aims and recruitment rate are achievable. The complex and poorly-understood nature of functional constipation, combined with the nature of the treatment itself, has necessitated a pragmatic approach with several compromises being made to try to ensure that the study is feasible.

From a methodological perspective, the fact that neither participant nor assessor blinding was feasible (due to the nature of the treatment and the nature of the outcome data being collected), leads to the possibility of performance bias and reporting bias, as both participants and assessors will (consciously or unconsciously) have particular pre-conceived ideas about the likely efficacy of each system. In the qualitative interviews, several participants alluded to this, and described being pleased or disappointed with their allocated system. Attempts have been made, from a methodological and operational perspective, to limit the impact of this. The fact that every patient gets treatment is important, as it is a reasonable assumption that the placebo effect for each system is similar (this is an advantage over a 'matched controls' trial design), thereby meaning that any observed difference between systems is a genuine one. Additionally, the option of switching systems after three months is designed to allow participants who have not had success with their original system to try the other one. This means that patients do not spend too long on ineffective treatment, and also allows longer-term data (>3 months) to evaluate the effectiveness of the treatment as a whole in the long term.

A further measure to limit the impact of bias was to conceal the primary outcome questionnaire in a sealed envelope, thereby preventing the assessors from quantifying the improvement in PAC-QOL at each visit. Initially, this led to problems with questionnaires not being adequately completed, and in response to this the process was modified to allow brief review of the questionnaires before concealment to ensure they are completely filled in. This did not compromise the principle of concealment as the questionnaire is not meaningful unless the score is added up and compared with previous scores.

In summary, therefore, it can be said that although aspects of the study methodology represent a compromise in terms of blinding and outcome assessment, CapaCiTY 02 is nonetheless a robustly-designed study with the potential to fully answer the relevant research questions if conducted as per the study protocol.

Although the methodology employed during the course of this feasibility study is robust, there are many factors that limit the nature of the conclusions that can be drawn from it. The principle limitation of this study is the fact that the numbers of participants included is small. Although a fully-powered study with analysis of the complete outcome framework is outside the scope of this thesis, the delays in recruitment resulted in a smaller study sample than was initially planned. This has led to a feasibility study that is perhaps more limited and less powerful than it otherwise might have been. One manifestation of this has been the fact that a single

(possibly anomalous) PAC-QOL result at 1 month has skewed the overall result, giving the impression of a sharp initial drop in PAC-QOL at 1 month which then partially reverses after 3 months. It is impossible to say at this stage whether this is a genuine pattern or whether it is the product of an anomalous result. The full, adequately-powered study results will confirm or refute this.

Another consequence of the low study numbers recruited is that the pool of patients from which to draw candidates for qualitative interviews was smaller than hoped for. Although sufficient participants were interviewed after 1 month for data saturation to be reached for this time point, a far smaller number of participants had reached the 6-month time point and therefore the numbers interviewed were small. In particular, no interviews took place with participants after switching therapy, meaning that little has been gleaned regarding the experiences of these patients. Nonetheless, the three interviews conducted after 6 months did provide a number of interesting themes and concepts which can be explored further at other sites as the study progresses.

A further limitation of the qualitative arm of the study is that the interviewer was also a clinician involved in treating the patients. Although it was recognised that this could potentially affect the dynamic of the interview and steps were taken to minimise the impact of this (see Chapter 4, section 4.12), this nonetheless represents a compromise. For example, participants may have felt less able to express critical or negative views about the clinical team or the treatment they

received. The very positive comments made by participants about the irrigation nurses and clinical team must be interpreted in light of this.

7.6 WHAT COULD HAVE BEEN DONE DIFFERENTLY?

Having reviewed the results of this feasibility study, it is apparent that, while the trial design appears sound and the recruitment rate at the Durham site is on target, there are several areas which could have been improved upon.

Firstly, the delays in recruitment experienced at many sites were in part due to differences between the trial-specified training regime for trans-anal irrigation and local practices. Feasibility questionnaires were sent to each site and the results used to design the training regime (see Chapter 5, section 5.2). However, on reflection this questionnaire was not detailed or specific enough to highlight many of the problems which later emerged. This highlights the importance of conducting appropriately rigorous feasibility work before committing to a particular trial design.

Another major reason for recruitment being delayed was due to difficulty obtaining high-resolution manometry equipment (required for INVEST in the original protocol) at many sites. This was rectified by amending the protocol to allow standard manometry, however this introduced further delays and it would have been far easier if the nature of the potential problem had been identified at the planning

stage. These particular issues highlight some of the difficulties of multi-site working, and how close collaboration and communication with all participating sites is essential at each stage in order to design and run a trial appropriately.

Another potential area for improvement was as regards the number of outcome measures, and the duration of follow up. As demonstrated by the involvement of the constipation research advisory group (CRAG), the questionnaires evoked mixed responses; some (notably the Rome III questionnaire and MYMOP) were seen as difficult to complete, and not relevant. There were also concerns expressed about the total length of time required to complete the baseline questionnaire booklet. Following consultation with the trial steering committee, the total follow up duration was reduced from 24 months to 12 months, and the number of questionnaires was reduced. However, this required a major protocol amendment. A smaller and more focused set of outcomes, targeted to answer a more clearly-defined set of research questions, would have potentially improved matters in this regard.

The rate of completeness for patient diaries is also a concern highlighted by this study. As previously noted (section 7.3), the protocol includes several strategies for improving diary completion (namely a telephone call to the patient, or an email, 2 weeks before the study visit). However these have so far not proven practical; participants frequently have not answered the telephone, and there have been some technical difficulties with the REDCAP system which are yet to be fully

resolved. One further possible reason for the poor completion of diaries is the potential for confusion between the various patient-held documents; the 'Patient Journal', 'Irrigation Journal' and 'Patient Diary'. Although the PPI consultation had not identified any concerns with these documents, over the course of the study there were cases of participants losing the documents, or mixing them up. Reducing the number of patient-held documents (for example, using the irrigation journal only), or synthesizing the key information into a single journal, may have helped to reduce these problems. It remains to be seen whether the improvements to the online system will lead to an improved rate of diary completion.

7.7 WHAT FURTHER RESEARCH IS NEEDED?

There are many unanswered questions concerning the use of trans-anal irrigation therapy in chronic constipation, and the current evidence base for its use is weak. Nonetheless, there is trial evidence that it can be effective, as outlined in chapter 2 and in section 7.4 above. Given the complex and poorly-understood nature of chronic constipation, it is necessary to conduct a trial which not only determines the overall effectiveness of treatment, but also attempts to identify patient groups in whom it is especially effective. This will enable a more focused, targeted approach to therapy, and reduce the time patients spend trying ineffective treatments.

The CapaCiTY programme as a whole aims to construct a rigorously evidence-based treatment algorithm for patients with chronic functional constipation. If successful,

this will provide a valuable resource for clinicians dealing with this condition, and will lead to more effective and more cost-effective therapy. CapaCiTY 02, with its specific focus on trans-anal irrigation therapy, aims to answer important questions about the comparative effectiveness of each irrigation system as well as the effectiveness of the treatment in general. Additionally, the planned analysis of pre-treatment symptom profiles and radio-physiological characteristics will enable conclusions to be drawn regarding which types of patients derive the most benefit from irrigation, and which system they should use. These findings could form the basis of more focused research in this area.

The qualitative component of this study has yielded valuable information regarding the lived experience of patients commencing treatment with trans-anal irrigation, and this needs to be expanded on to include a broader range of participants with a more diverse range of experiences, especially at the 6 month time point. The CapaCiTY 02 study protocol includes interviews not only with patients at the 1 and 6 month time points, but also with health professionals involved in irrigation training. This study, conducted nationally, should provide a very rich description of the nature of the lived experiences of trans-anal irrigation therapy from patients' and health professionals' perspectives.

One final aspect of the feasibility analysis that may merit further investigation is the apparent lack of correlation in some patients between reported treatment

effectiveness (expressed during qualitative interviews) and the measured efficacy (the reduction in PAC-QOL). This raises interesting questions about patients' perception of treatment success and how this relates to their own personal experiences of illness. It also highlights the limitations of using numerical scores as a primary outcome measure in a study looking at a very complex and heterogenous illness. Furthermore, this demonstrates the value of the mixed-methods approach employed in this study, and illustrates how both qualitative and quantitative elements of a study can combine effectively to build up a more nuanced picture of the nature of a treatment's therapeutic benefits than would be possible through quantitative analysis alone.

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Appendix I: Study Protocol and ethical approvals

- **CapaCiTY 02 Study Protocol**
- **Research Ethics Committee approval**
- **Research Ethics Committee Substantial Amendment approval**
- **Durham University Chair's Action Approval**
- **Durham University Chair's Action approval of amendment**

Full Title

PRAGMATIC RANDOMISED TRIAL OF LOW VERSUS HIGH VOLUME INITIATED TRANSANAL IRRIGATION THERAPY IN ADULTS WITH CHRONIC CONSTIPATION

Short Title/Acronym	**Chronic Constipation Treatment Pathway, Study 2** **CapaCiTY02**
Lay title	**Low volume versus high volume anal irrigation therapy for the treatment of adults with chronic constipation.**
Sponsor	*Queen Mary, University of London* *Contact person of the above sponsor organisations is:* *Sally Burtles* *Director of Research Development* *Joint Research Management Office* *5 Walden Street* *London* *E1 2EF* *Phone: 020 7882 7260* *Email: sponsorsrep@bartshealth.nhs.uk*
REC Reference	15/LO/0732
Funding Reference	PGfAR: RP-PG-0612-20001

REDA number	010509
PCTU Reference	P127
IRAS	172401
ISRCTN	**ISRCTN11093872**

Chief Investigator	*Professor Charles Knowles*
Coordinating Centre	National Centre for Bowel Research and Surgical Innovation, Barts and the London School of Medicine and Dentistry.
Funding	NIHR Programme for Applied Research

Recruiting sites (initial)

- Barts Health NHS Trust [Allison]
- St Marks Hospital at London North West Healthcare NHS Trust [Vaizey]
- University College Hospital London [Emmanuel]
- Guys and Thomas' Hospitals London [Williams]
- Sandwell and West Birmingham NHS Trust [Gill]
- County Durham and Darlington NHS Foundation Trust [Yiannakou]
- University Hospital Southampton NHS Foundation Trust [Nugent]
- Norfolk and Norwich University Hospitals NHS Foundation Trust [Speakman]
- University Hospital of South Manchester NHS Foundation Trust [Telford]
- Sheffield Teaching Hospital NHS Foundation Trust [Brown]
- North Bristol NHS Foundation Trust [Dixon]
- University Hospitals Bristol, NHS Foundation Trust [Mabey/Randall]
- Newcastle Upon Tyne, NHS Foundation Trust [Plusa]
- Homerton University Hospital, NHS Foundation Trust [Cuming]

Reserve Sites

-
- University Hospital Leicester NHS Foundation Trust [Miller]

Central facilities

- Bart's and the London, Pragmatic Clinical Trials Unit. Centre for Primary Care and Public Health, Queen Mary University London (QMUL).
- County Durham and Darlington NHS Foundation Trust, Durham Clinical Trials Unit. Wolfson Research Institute, Durham University.

1. GLOSSARY OF TERMS

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
BD	Twice per day
B IPQ	Brief Illness Perception Questionnaire
BNF	British National Formulary
CC	Chronic Constipation
CI	Chief Investigator
CPCPH	Centre for Primary Care and Public Health
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
EC	European Commission
EQ-5D	EuroQol Health Outcome measure
EQ-VAS	EuroQol Visual Analogue Scale
FDD	Functional Defaecation Disorder
GAD7	Generalized Anxiety Disorder Questionnaire
GAfREC	Governance Arrangements for NHS Research Ethics Committees
HT	Habit Training
HTBF	Habit Training Incorporating Direct Visual Biofeedback
HRA	Health Research Authority
ICF	Informed Consent Form
INVEST Function	Standard Panel of Radio-Physiological Tests of Colonic and Anorectal
JRMO	Joint Research Management Office
LTF	Lost To Follow-up
NDUHT	North Durham University Hospital Trust
NHS REC	National Health Service Research Ethics Committee

NHS R&D	National Health Service Research & Development
PAC-QOL	Patient Assessment of Constipation Quality of Life questionnaire
PAC-SYM	Patient Assessment of Constipation Symptoms Questionnaire
Participant	An individual who takes part in a clinical trial
PCSG	Primary Care Society for Gastroenterology
PCTU	Pragmatic Clinical Trials Unit
PHQ-9	Patient Health Questionnaire -9
PI	Principal Investigator
PIS	Participant Information Sheet
PMG	Programme Management Group
PPIG	Patient and Public Involvement Group
PRO	Patient Reported Outcomes
PSC	Programme Steering Committee
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RAIR	Rectoanal Inhibitory Reflex
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Document Verification
SOP	Standard Operating Procedure
TAI	Transanal Irrigation
TDS	Three Times Per Day
VAS	Visual Analogue Scale
WP	Work Package Signature Page

2. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 3.0, dated 22Jan2016)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Prof Charles Knowles

Chief Investigator Site: Barts Health NHS Trust

Signature and Date:  **22Jan2016**

Principal Investigator Agreement *(if different from Chief investigator)*

The clinical study as detailed within this research protocol **(Version 3.0, dated 22Jan2016)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

Statistician Agreement

The clinical study as detailed within this research protocol **(Version 3.0, dated 22Jan2016)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World

Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Statistician Name: Professor Sandra Eldridge

Principal Investigator Site: PCTU

Signature and Date: **22Jan2016**

3. SUMMARY/SYNOPSIS

Short Title	CapaCiTYstudy2
Methodology	Pragmatic randomised trial comparing low volume with high volume initiated anal irrigation therapy in adult patients with CC who have not responded to nurse-led biofeedback or bowel habit training.
Research Sites	NHS Trusts in England focussing on specialist pelvic floor centres; primary care networks in England; trial oversight by Pragmatic Clinical Trials Unit, Queen Mary University of London and Durham University.
Objectives/Aims	To determine: (1) The impact upon patient disease specific quality of life of transanal irrigation (TAI) initiated with a low-volume (LV) versus high-volume (HV) system in patients with CC. (2) Survival (continuation of benefit) and acceptability by type of system. (3) The influence of patient characteristics (urge to defaecate, balloon sensory testing results) upon treatment success, and response by type of system used. (4) Strategies for tailoring treatment to patients' symptoms and acceptability of each system to patients. (5) The safety of each system. (6) The cost-effectiveness of care.
Number of Patients	300 (1:1 allocation)
Main Inclusion Criteria	Chronic constipation in adults (18-70 years) as defined by pragmatic clinical criteria [self-reported symptom duration > 6 months; failure of laxatives and lifestyle modifications, failure of previous nurse led behavioural therapy].
Statistical Methodology and Analysis (if applicable)	A superiority trial design will test the null hypothesis that: • There is no difference in outcome (PAC-QOL) when initiating transanal irrigation with a low-volume or high-volume system after 3 months of therapy. Outcomes (at 3 6 and 12 months) will include: • PAC-QOL, PAC-SYM, EuroQoL measures, , GAD7, PHQ-9, global patient satisfaction, CC-BRQ, BIPQ (CC). • A survival curve of duration of benefit from treatment will be used as a further marker of treatment efficacy. • Pre-treatment patient characteristics informed by pathophysiological investigation (INVEST) will be used to assess the relationship between response to treatment and investigation results. A full analysis plan will be signed off before allocation codes are made available to the statistician. The standardised outcome framework being used across the CapaCiTY

	programme of studies will be employed, including clinical and health economic outcomes as well as qualitative assessments.
Proposed Start Date	01.08.15
Proposed End Date	31.10.18
Study Duration	38 months

4. INTRODUCTION

4.1 Background

Burden of disease

Constipation is common in adults and up to 20% of the population report this symptom depending on definitions used[1-3], with a higher prevalence in women[145] and older people[67]. Chronic constipation (CC), usually defined as more than 6 months of symptoms, is less common[8] but results in 0.5 million UK GP consultations per annum. A proportion of the population suffer symptoms which are both chronic and more disabling (about 1-2% population)[9]. Such patients, who are predominantly female[10], are usually referred to secondary care with many progressing to tertiary specialist investigation. Patient dissatisfaction is high in this group; nearly 80% feel that laxative therapy is unsatisfactory[11] and the effect of symptoms on measured quality-of-life (QOL) is significant[12]. CC consumes significant healthcare resources. In the US in 2012, a primary complaint of constipation was responsible for 3.2 million physician visits[13] resulting in (direct and indirect) costs of $1.7 billion. In the UK, it is estimated 10 per cent of district nursing time is spent on constipation[14] and the annual spend on laxatives exceeds £80m, with 17.4 million prescriptions in 2012 (Health and Social Care Information Centre, 2013)[15].

Pathophysiological basis of chronic constipation

The act of defecation is dependent on the coordinated functions of the colon, rectum and anus. Considering the complexity of neuromuscular (sensory and motor) functions required to achieve planned, conscious, and effective defaecation[16] it is no surprise that disturbances to perceived 'normal' function occur commonly at all stages of life. Clinically, such problems commonly lead to symptoms of obstructed defaecation e.g. straining; incomplete, unsuccessful or painful evacuation; bowel infrequency; abdominal pain and bloating. After exclusion of a multitude of secondary causes (obstructing colonic lesions, neurological, metabolic and endocrine disorders), the pathophysiology of CC can broadly be divided into problems of

colonic contractile activity and thus stool transit and problems of the pelvic floor. Thus, with specialist physiological testing (hereafter referred to as INVEST in this protocol), patients may be divided into those who have slow colonic transit, evacuation disorder, both or neither (no abnormality found with current tests). Evacuation disorders can be then subdivided into those in which a structurally-significant pelvic floor abnormality is evident e.g. rectocele or internal prolapse (intussusception) and those in which there is a dynamic failure of evacuation without structural abnormality: most commonly termed 'functional defaecation disorder (FDD)'.

Chronic constipation management overview

Management of CC is a major problem due to its high prevalence and lack of widespread specialist expertise. In general, a step-wise approach is undertaken, with first line conservative treatment such as lifestyle advice and laxatives (primary care) followed by nurse-led bowel re-training programs, sometimes including focused biofeedback and psychosocial support (secondary/tertiary care). Although these treatments may improve symptoms in more than half of patients, they are very poorly standardised in the UK and are not universally successful[17]. Thus, patients with intractable symptoms and impaired QOL may be offered a range of costly, irreversible surgical interventions with unpredictable results[18, 19], sometimes resulting in major adverse events or a permanent stoma.

Overall rationale for the CapaCiTY programme

The current trial forms part of an NIHR-funded programme (PGfAR: RP-PG-0612-20001). This programme aims to develop the evidence base for the management of chronic constipation (CC) in adults which is currently lacking. This is in contrast to the management of CC in children for which NICE guidance has been recently published (http://pathways.nice.org.uk/pathways/constipation-in-children-and-young-people)[20, 21]; and for adults with faecal incontinence[22]. Thus the current situation is one where there are considerable variations in practice, particularly in specialist services. With a number of new drugs gaining or seeking NHS approval[23-26] and technologies at a horizon scanning stage[18, 27, 28]it is timely that the currently limited evidence base for adult CC is developed for resource-constrained NHS providers to have confidence that new and sometimes expensive investigations and therapies are appropriate and cost-effective. A cost-conscious pathway of care may help reduce healthcare expenditure by appropriately sequencing the care provided, while targeting more expensive therapies at those most likely to benefit. Such data will inform the development and commissioning of integrated care pathways. An overview of the CapaCiTY programme is provided as a scheme [APPENDIX 1] and includes a series of interlinked work packages (WPs) that answer the important questions for patient care. A rolling program of national recruitment will provide a large cohort of well-defined patients for subsequent studies within sequential WPs over 5 years. The focus will be on generating real life evidence from pragmatic studies which will

provide valid clinical outcome measures, patient acceptability and cost. Armed with such data it will be possible to develop an NHS management algorithm for CC which will meet patient, clinician and policy aims.

4.2 Specific clinical background to the prospective cohort study of anal irrigation

Anal irrigation, using a variety of commercially available devices, has been rapidly disseminated internationally over the past 3-5 years, first in patients with neurological injury [29, 30]and subsequently in other CC groups[31, 32]. Despite a lack of published data other than from small selected case series, it is now available on the drug tariff and generally considered to be the next step in patients failing other nurse-led interventions such as biofeedback. Anal irrigation has permeated the UK market without robust efficacy data and with on-going concerns regarding longevity of treatment and complications [29, 33]. Retrospective clinical audit data and review[33]suggest a continued response rate after one year of approximately 50% with such patients thus avoiding or delaying surgical intervention. An accurate assessment of response rate and acceptability of this intervention requires confirmation in a large prospective cohort, together with clinico-physiological predictors of success. In addition, two alternative systems for delivery of trans-anal irrigation exist; low-volume systems delivering approximately 70ml per irrigation, and high-volume systems delivering up to 2 litres of irrigation (although typically only 0.5 – 1.5 litres is required per irrigation). The low-volume system is cheaper, costing approximately £750 p.a. based on alternate-day use, compared with approximately £1400-1900 for high-volume irrigation, and may be more acceptable to patients, and so a randomised study comparing the two systems is needed.

4.3 Rationale and Risks/Benefits

Robust data for the use of anal irrigation therapy in chronic (idiopathic) constipation are lacking. In addition, there are no data demonstrating superiority of high-volume irrigation over low-volume systems. Given the differences in cost between the two systems, a randomised study of well-characterised patients comparing the two methods would provide useful information on whether one system holds a clear advantage over the other. Also, the short- and long-term efficacy and acceptability of therapy in chronic constipation could be evaluated. This is timely and informative given the rapidly increasing popularity of this treatment and the fact that anal irrigation is an invasive therapy for which patient selection should also be optimised to maximise benefit.

In practice, patients will use one system only (plus defined ‘rescue therapies’ – see below) for a minimum of three months. After this time point they may switch to the other system if their initial therapy was ineffective/unsatisfactory. Thus consenting patients will be randomised to initiate therapy with one of these systems but will have the option of switching to the other after an initial three-month period. This allows us

to identify response rates to each system in the short term (three months), and thereafter this study is a comparison between treatment strategies (low-volume initiated therapy versus high-volume initiated therapy) rather than a pure comparison of the two techniques. This is a patient-centred study design aiming to limit the time patients spend using ineffective therapy without being allowed to try an alternative. This also allows estimation of comparative cost-effectiveness of the two treatment pathways, and whether one system works better depending on the radio-physiological profile of the patient. Recent data estimates approximately 85% of patients are still using irrigation at 1 month; this represents a significant short-term treatment failure rate [34]. Once patients have switched therapy, they may not switch back to the first system; once they have tried both systems and discontinued them then they will be considered to have completed the intervention and they will return to routine clinical care.

Patient and Public Involvement (PPI) consultation with current patients in secondary care with this condition has explored the acceptability of this study design to patients, and we have found that this is likely to be acceptable. The study design, proposed rescue therapy and patient diaries/journals have been reviewed as part of this process.

Irrigation is a maintenance therapy rather than a cure. In addition to outcome measures of PAC-QOL score at three months, patients will provide survival data (time until cessation of irrigation therapy due to lack of benefit). Switching systems does not affect this; the survival data is based on use of irrigation irrespective of system. A survival analysis is appropriate since anal irrigation is time-consuming and inconvenient as a therapy and patients may find the process distasteful. Patients are unlikely to continue with treatment if they are not gaining worthwhile benefit from it; treatment continuation is a useful patient-centric assessment.

Consideration of the findings from both groups (individually and together) will be used to model the net value to patients of anal irrigation, considering persistence of benefit.

The risk of non-participation is considered very low. The interventions proposed are those already offered to patients in specialist centres throughout the UK and internationally. All interventions pose acceptable and minimal risks. For instance, the only invasive tests (INVEST) have been performed daily in most specialist centres for up to 30 years without any recorded complication (Barts Health experience > 10,000 patients). A small ionising radiation dose is required for two tests (covered below). A number of questionnaires contain personal questions about bowel problems and the effect of these on quality of life and psycho-behavioural functioning, however all have been used in studies of similar patients previously.

Risks of anal irrigation therapy

Trans-anal irrigation has been shown to be a low-risk intervention and is widely used in a variety of defecatory disorders such as neurogenic bowel dysfunction, idiopathic constipation and faecal incontinence. Serious adverse events are rare, with one study reporting 2 non-fatal bowel perforations out of approximately 110,000 irrigation treatments [29]. Other potential side effects include pain, bleeding, painful haemorrhoids and anal fissure. A recent study reported an overall adverse event rate of 22% when all minor and reversible events were considered.13% reported technical problems with equipment and 13% reported minor side effects/adverse events[34].

The benefits of participation are that patients will receive a very high standard of monitored care as a consequence of the detailed protocol. Participation will inform future treatment options for patients with chronic constipation

5. TRIAL OBJECTIVES

5.1 Primary objectives

2. To compare the impact upon patient disease specific quality of life of transanal irrigation initiated with a low-volume versus high-volume system in patients with chronic constipation, measured at 3 months.

5.2 Secondary objectives

To determine:

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7. Survival (continuation of benefit) and acceptability in the longer term (up to 12 months).
8. Disease specific outcomes at 3 6 and 12 months
9. The influence of patient characteristics (urge to defecate, balloon sensory testing results) upon treatment success, and response by type of system used.
10. The acceptability of each system to patients.
11. Strategies for tailoring therapy to meet patients' individual needs, and the factors involved in this.
12. The safety of each system and prospective tracking of AEs.
13. The cost-effectiveness of care.
14. To qualitatively evaluate patient and health professional experience for interventions.

5.3 Endpoints

Clinical endpoints

All clinical endpoints will be in common with a single standardised outcome framework (consistently used within all CapaCiTY programme studies). All outcomes will be recorded at baseline, 3, 6 and 12 months in face-to-face clinics (or by telephone call if necessary). PAC-QOL, PAC-SYM and EQ-5D-5L, EQ-VAS will additionally be collected at 1 month; this is to capture reasons for early non-response to therapy, as well as to better characterise the patients group and provide more data for economic analysis. The primary endpoint will be at 3 months.

Primary Clinical Outcome

- .Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL[35, 36]) at 3 months

Secondary Clinical Outcomes

- PAC-QOL score and individual domain scores at 1, 3, 6, and 12 months
- Time to cessation of each system of irrigation; total time in treatment with either system (from irrigation journal) at 1, 3, 6, or 12 months.
- Reason for cessation (of each system) (irrigation journal and qualitative interviews) at 1, 3, 6, and 12 months.
- Patient Assessment of Constipation Symptoms (PAC-SYM): aggregate and domain scores at 1, 3, 6, and 12 months.
- Volume and duration of irrigation (irrigation journal) at 1, 3, 6, and 12 months.
- Number and nature of bowel motions (captured in 2-week patient diary) at 3, 6 and 12 months
- Symptom scores derived from diary records (taken over two weeks before or around each follow-up contact. These will include number of spontaneous complete bowel motions at 3, 6 and 12 months
- .
- Generalized anxiety disorder questionnaire (GAD7) at 3, 6 and 12 months
- Depression, anxiety and somatisation modules of the PHQ-9 at 3, 6 and 12 months
- Global patient satisfaction / improvement score (VAS) at 3, 6 and 12 months
- Patient acceptability and recommendation to other patients (qualitative interviews) see section 7.16
- Behavioural response to illness questionnaire (CC-BRQ), and brief illness perception questionnaire BIPQ (CC) at 3, 6 and 12 months
- Generic quality of life: EuroQol EQ-5D-5L and EQ-VAS scores 1, 3, 6, and 12 months.
- Use of healthcare resources, adverse events, and concomitant medications (collected using patient journal) at 3, 6, and 12 months

Health economic outcomes

- Interventions, treatment sequelae and other health resource use related to the care of CC will be recorded in natural units and cost applied where possible using national reference costs. Additionally, patient costs related to constipation and the opportunity cost of time away from normal activities will be valued using national reference sources.

Patient experience (See section 7.16: Qualitative interviews)

- Face-to-face, digitally recorded, semi-structured interviews will be conducted involving a purposive, diverse sample of patients throughout the programme, with participants reflecting a range of ages, geographical locations, and where possible other pertinent attributes such as ethnicity and gender, continuing until data saturation when no new themes emerge. Participants will be approached by a member of the research team and will undergo a separate consent process if they are willing to participate in the qualitative study.

6. METHODOLOGY

6.1 Inclusion Criteria

- Age 18-70 years.
- Patient self-reports problematic constipation.
- Symptom onset > 6 months before recruitment.
- Symptoms meet American College of Gastroenterology definition of constipation.
- Non-response to constipation treatment to a minimum basic standard (see NHS Map of Medicine 2012)[37]: Comprising lifestyle AND dietary measures AND ≥2 laxatives or prokinetics tried (no time requirement) [APPENDIX II].
- Ability to understand written and spoken English (due to questionnaire validity).
- Ability and willingness to give informed consent.
- Failure of previous nurse-led behavioural therapy.
- Ability of patient/carer to use anal irrigation.

The study will use the American College of Gastroenterology definition of constipation[38]

(which is reasonable, simple and extensively published): unsatisfactory defaecation characterized by infrequent stool, difficult stool passage or both for at least previous 3 months. This avoids the more complex Rome definitions (which are likely to change with Rome IV in 2015).

6.2 Exclusion Criteria

The study interventions necessitate the exclusion of major causes of secondary constipation. In detail;

- Significant organic colonic disease (red flag' symptoms e.g. rectal bleeding previously investigated); IBD; megacolon or megarectum (if diagnosed beforehand) [the study will provide a useful estimate of the prevalence of such cases in referral practice]; severe diverticulosis/stricture/birth defects deemed to contribute to symptoms (incidental diverticulosis not an exclusion).
- Major colorectal resectional surgery.
- Current overt pelvic organ prolapse (bladder, uterus, vagina, rectum) or disease requiring surgical intervention.
- Previous pelvic floor surgery to address defaecatory problems: posterior vaginal repair, STARR and rectopexy; previous sacral nerve stimulation.
- Previous use of transanal irrigation therapy to treat constipation.
- Rectal impaction (as defined by digital and abdominal examination: these form part of the NHS Map of Medicine basic standard)[37.]
- Significant neurological disease deemed to be causative of constipation e.g. Parkinson's, spinal injury, multiple sclerosis, diabetic neuropathy (not uncomplicated diabetes alone).
- Significant connective tissue disease: scleroderma, systemic sclerosis and SLE (not hypermobility alone).
- Significant medical comorbidities and activity of daily living impairment [based on Bartell index in apparently frail patients[39], Barthel index <=11].
- Physical disability/impairment which prevents use of one or other of the irrigation devices.
- Major psychiatric diagnosis [schizophrenia, major depressive illness, mania, self-harm, drug/alcohol addiction].
- Chronic regular opioid use (at least once daily use) where this is deemed to be the cause of constipation based on temporal association of symptoms with onset of therapy; all regular strong opioid use.
- Pregnancy or intention to become pregnant during study period.

NOTE: Red flag symptoms are not an exclusion if they have been investigated before enrolment and organic disease excluded. Previous transanal irrigation therapy does not include private (non-NHS) 'colonic irrigation' therapy; prior use of such treatments is not an exclusion criterion.

6.3 Study Design / Plan – Study Visits

6.3.1 Setting

Specialist centres across England with a mix of urban and rural referral bases.

6.3.2 Recruitment

Patients attending specialist centres (outpatient clinics, GI physiology units) for constipation and who have already failed to respond to a minimum basic standard of treatment (see above), as well as nurse-led interventions (biofeedback or habit training) will be eligible for recruitment screening based on criteria. Patients will be recruited from those failing treatment in CapaCiTY01 but also those patients seen outside the trial who have had nurse led behavioural therapies without response.

Trial posters will be displayed in primary care and community care settings, directing patients to their nearest research site and contact person, as well as the study

website for more information, including the patient information sheet. The same posters may be used to advertise the study via the internet and social media.

6.3.3. Visit 0: Pre-Screening: Eligibility assessment

A GCP-trained and delegated local researcher will screen for basic eligibility by phone (or face-to-face interview based on patient choice). Potentially eligible patients will be identified either in clinic, from referral letters from GPs/other consultants to the constipation clinic, and from patients participating in CapaCiTY01 who did not respond or have ceased to respond to habit training/biofeedback. Participants will be provided with adequate explanation of the aims, methods, anticipated benefits and risks of anal irrigation therapy and will take away or be posted an invitation letter and a patient information sheet. Patients will be given at least 24 hours to consider participation and invited to attend clinic for Visit 1 (see below).

The study screening number will be allocated as follows:
Study Code 02
Site Code – 3 letter code for each site (APPENDIXIII)
Participant Code – 4 digit code given consecutively and attributed at each site

For example the first participant recruited at Barts Health Trust would be assigned the code 02-BLT-0001.

Patients progressing to other studies within the CapaCiTY programme will keep this number for pathway tracking.

6.3.4 Visit 1: Screening, consent and baseline assessments

Visit 1 will be conducted face to face in clinic. Following a detailed discussion about the trial, potentially eligible and agreeable patients will complete written informed consent, followed by a more thorough screening and confirmation of eligibility for randomisation by brief history and physical examination (the latter if not already performed within the previous 3 months).

Patients who decide not to opt for treatment will be invited to offer reasons and these will be recorded when provided. Patients declining participation will continue to receive usual care as locally provided. There is no obligation for patients to give reasons for non-participation.

For those patients entering the study, additional baseline outcome assessments will be conducted. These include several key validated assessments that profile patient characteristics, informing disease pathophysiology and potential predictors of treatment response. All have been selected on the basis of trade-off between adequate detail and achievable brevity. These instruments will be combined into a single booklet (design and presentation have been optimised by patient representatives).

<u>Confirmation of Eligibility</u>

<u>Screening/Confirmation of Eligibility</u>

- Standardised history by interview including previous medication usage.
- Clinical examination findings (carried forward if performed previously within last 3 months): standardised exam of perineum/anus/rectum.

Baseline outcome assessments

- Baseline outcome assessments [PAC-QOL, PAC-SYM,, EQ-5D-5L & EQVAS, PHQ9, GAD7, CC-BRQ and BIPQ-CC, see endpoints above].
- Baseline 2-week patient diary will be given. Training in completion of the diary will be conducted at visit 1 and the diary will be completed at home and returned at visit 2.
- Training and retrospective completion of the patient journal will occur at visit 1 for collection of resource data. Prospective completion will occur continuously, with review at each follow up visit from 3 to 12 months.

Other baseline only assessments

- Constipation (2006) and IBS (2006) modules of Rome III questionnaire.
- Cleveland Clinic constipation questionnaire.
-
- Brief, chronic pain, autonomic and joint hypermobility assessments.
- St Marks Incontinence score (for concurrent symptoms).

Randomisation to be conducted by a member of the research team

INVEST radio-physiology investigations (See section 7.5.3): There is no defined time period for this, but it is suggested INVEST should be completed within 4 weeks of Visit 1 baseline visit to allow for diary completion before stopping laxatives for INVEST. A maximum of 8 weeks tolerated to conduct INVEST.

Those with INVEST completed in the previous 12 months do not need these repeated and can be booked for visit 2, commencing in minimum of 2 weeks to allow completion of baseline diary.

6.3.5 Visits 2-3: Interventions

Visit 2:

- Collection of baseline diary completed before stopping laxative (i.e. before INVEST in patients who need this done).

- Training in Anal Irrigation - Patients will undergo a single nurse-led training session before starting treatment.

- Training in completion of irrigation journal and provision of irrigation journal to be completed weekly. The irrigation journal consists of, volume of water introduced, frequency of use adverse events and side effects e.g. pain, bleeding.

- Start date for home irrigation agreed with the patient (this is to allow for any delay in delivery of equipment). Ideally this should be the same day as Visit 2, or within 1 week maximum. If any issues or delays have been encountered, a new commencement date is agreed; This should be recorded as a deviation/note to file (CRF 7/8), along with reasons for delay

.

Visit 2.1
Patients will be contacted by telephone 14 days (+/- 3 days) after Visit 2 to ensure no problems have been encountered including a review of adverse events and concomitant medications.

Visit 2.2 (if needed)
If there are problems then a further face-to-face training session will be offered, including a review of adverse events and concomitant medications. This can occur any time before visit 3 (2 weeks +/- 1 week from visit 2.1) or in conjunction with visit 3 if not before.

Patients will continue the self-administered therapy using a commercially-available device until the end of the study. Patients will be followed up until the end of the data collection phase of the study (variable follow up 12-24 months depending on date of recruitment) or until they decide to discontinue either the therapy or the trial follow up. Irrigation will be performed at an agreed frequency initially (see section 7.5.2). Once established on this therapy patients may adjust the frequency and volume of irrigation to suit their particular condition.

Information about treatment will be recorded in an irrigation journal. This information shall consist of: frequency of use of irrigation; volume of water introduced; adverse events and side effects e.g. pain, bleeding. Where a patient switches to the other irrigation device or discontinues treatment (patient choice) the reason for this, as well as the duration of therapy, will be documented. If a patient chooses to switch devices, which they may do at any stage after the 3 month follow up visit, they will receive training in the other device. They will receive a follow up by the irrigation nurse as required to resolve any outstanding issues and to check progress. This should be documented on the irrigation journal and a note to file, (CRF 8) and change/discontinue, (CRF 12) should be completed. However they will not be asked to repeat the questionnaires and diaries already completed at 1 and 3 months.

Visit 3
This takes place 2 weeks (+/- 1 week's tolerance if needed) after Visit 2.1. PAC-QOL, PAC-SYM and EQ-5D-5L will be recorded at this visit, and irrigation journal is reviewed. A new patient diary, journal and irrigation journal are provided for collection at next follow up visit.

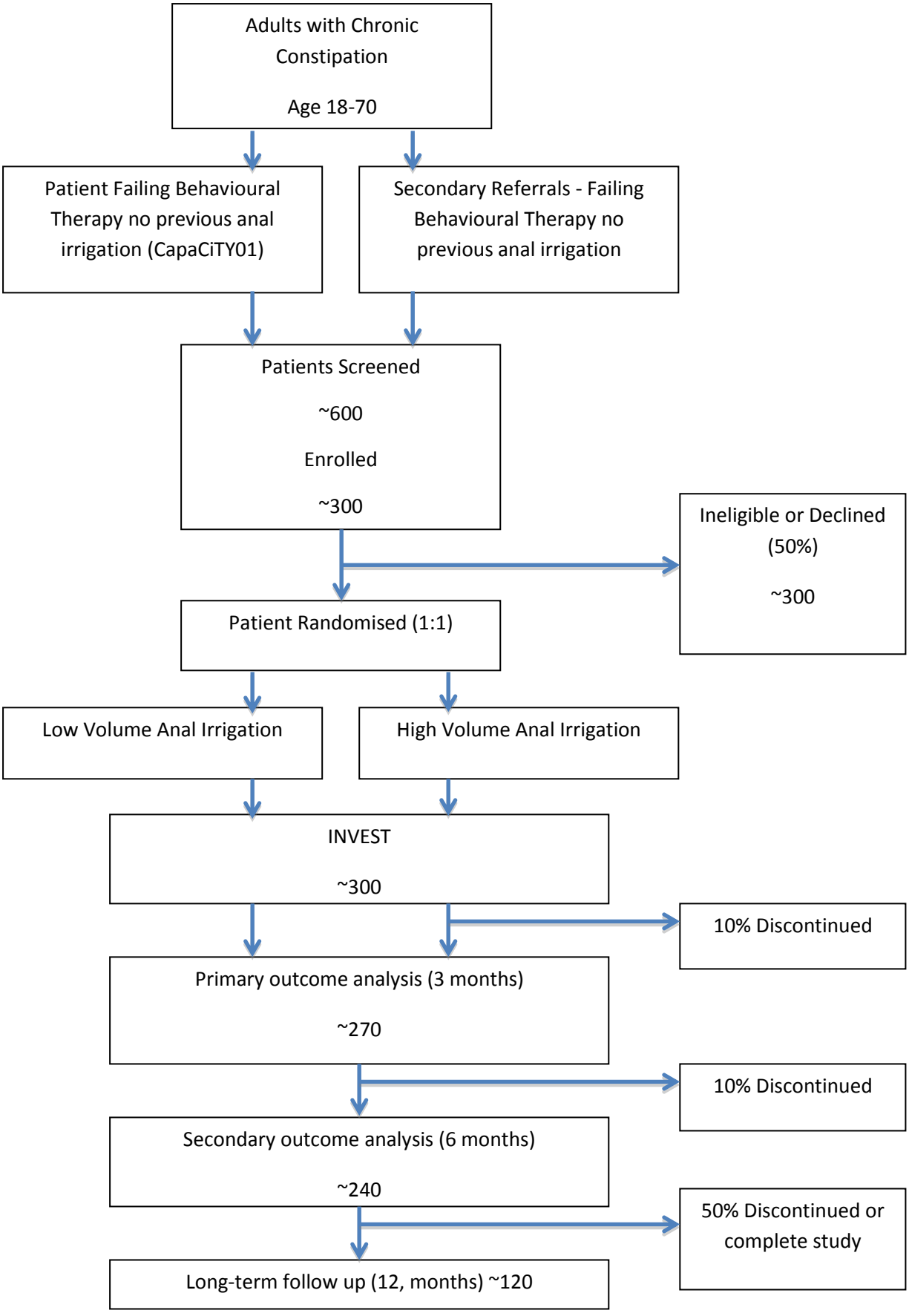
6.3.6 Visits 4-6: Follow-up outcome assessments: visits or telephone consultations

A full standardised outcome framework and health economic dataset will be recorded at baseline, 3, 6 and 12 months (+/- 1 week) after initiation of intervention at Visit 2. To maximise completeness of data collected, follow up visits will be conducted face-to-face in clinic wherever possible. Where this is not possible, a telephone consultation will be used.

The patient diary and journal and irrigation journal will be provided for review at each follow up visit.

Within the follow up period at least 3 attempts via 2 different methods (e.g. phone and letter), will be made by research staff to make contact and collect follow up data at each time point, after which the time point will be recorded as missing

6.3.7 Study Scheme Diagram



7. STUDY PROCEDURES

7.1 Informed Consent Procedures

Written informed consent will be obtained at visit 1 from research participants by an appropriately trained and delegated researcher in a face to face setting in clinic.

7.2 Screening, Enrollment

A brief screening questionnaire will be used to determine whether patients meet inclusion and exclusion criteria (see eligibility above). Screening will be performed by suitably trained study personnel to minimise logistic hurdles, and as determined by geographic availability.

The brief screening questionnaire will also be made available on the study website, with the participant information sheet for patients to self-screen and contact their nearest research site if interested in taking part. All basically eligible participants will then undergo formal face to face consent, screening and enrolment session prior to randomization.

7.3 Randomisation Procedures

Patients will be randomised 1:1 into two groups; those who commence therapy with a low-volume device and those starting with a high-volume device. Patients will be stratified by sex and females by centre. Randomisation will be performed by a GCP-trained member of the research team using an online system.

7.4 Blinding

Patients and clinicians are necessarily aware of both INVEST and treatment allocations. The need to collect data on frequency and volume of irrigation, as well as reasons for discontinuing or switching between systems, means assessor blinding is not possible with respect to these outcomes. Any researcher collecting CRFs or handling journals will therefore be unblinded. However, the primary outcome (PAC-QOL at three months) will be concealed; the patients will complete this questionnaire without a researcher present. This will be accomplished in one of the following ways;

1. Direct entry to online secure database, with built in validation and prompting to ensure data completeness.

2. Completing paper questionnaire by following instructions on an information card to ensure all questions are answered. This will be placed in a sealed envelope marked with the patients pseudonymised study code and will not be opened until the time comes for data entry.

7.5 Study interventions

7.5.1 Anal Irrigation therapy

Anal irrigation training will be provided by trained nurse or physiotherapist with experience in delivering care for chronic constipation. They must have initiated irrigation therapy in at least three patients independently, and be a nurse/therapist of good standing within a clinical team regularly seeing patients with chronic constipation. A standardised approach and intervention will be provided via use of an intervention manual. For the first three months of participation in the study, patients may not use other therapies besides anal irrigation and those rescue therapies specified below. They may discontinue therapy at any point (elective withdrawal from intervention) and may switch from one system to the other after 3 months. Switching anal irrigation systems before completing the three-month waiting period will be discouraged. If it does occur, it will be documented as a protocol violation with the timing and reason documented. If symptoms are severe despite use of irrigation and rescue therapies then other medications may be used on compassionate grounds, but this must be recorded in the CRF/concomitant medications log.

The course of therapy will include a nurse-led training session (or more if required to ensure the device is being used effectively) followed by patient-led home irrigation therapy. The low-volume system commonly used in practice is Qufora® Mini (MBH-International). Various high-volume systems are used, all of which have very similar mechanisms of action; these include Peristeen™ (Coloplast) and Qufora-Toilet/Qufora-Balloon™ (MBH-international).

These are commercially-available transanal irrigation systems available on prescription in NHS practice.

Low-volume Irrigation
This system consists of a small reservoir attached to a cone. The reservoir holds approximately 70ml of water and is squeezed to inject water into the rectum. The regime used will be as follows: Initial irrigation once daily for 14 days using 1 -3 insufflations (each of 70ml approximately). This may then be reduced to alternate days depending on response. Patients may then adjust frequency and volume depending on response. They may irrigate as much and as often as they feel is necessary to give them benefit and this information will be captured on the CRF with the aid of an irrigation journal.

High-volume irrigation
High-volume systems consist of an irrigation bag connected to a tube. The water flows into the rectum, either by gravity or using a pump. Some systems employ a balloon to hold the device in place during irrigation; others require the patient to hold it in place. The mechanism of action is the same for all systems. Initial frequency of irrigation is the same as for low-volume irrigation; i.e. daily for 14 days, then alternate days. Patients will commence with irrigations of 300ml and increase this by 100 ml every two days until satisfactory defaecation is achieved or the procedure becomes uncomfortable, up to a maximum of 1500ml. Patients may adjust therapy depending on response, as for low-volume irrigation.

Training sessions (45-60 min) (V2-V3)
This will use a standardised proforma and will always be face to face. Patients will receive:
Visit 2:

(i) Regulation/standardisation of laxative use: Bisacodyl may be used orally as a rescue therapy (up to 20mg at night), plus glycerine suppositories 1-2 if needed, if no stool for 3 days. In addition, patients may take Movicol up to a maximum dose of 2 sachets three times per day (TDS) and/or lactulose up to 15ml twice per day (BD). Prokinetic drugs and any other drug that the British National Formulary (BNF) describes as having laxative effect or herbal teas that contain strong purgatives will be discouraged, but if needed (i.e. if symptoms severe) then these are permitted but use must be recorded in the concomitant medications log. There will be no use of enemas.
(j) The device will be demonstrated to the patient by the nurse specialist and then the patient will practice setting up the device. The trainer will ensure the patient knows how to use the device correctly before home irrigation is commenced. The trainer and patient will agree a date for delivery of equipment and commencement of home irrigation. Ideally this should be the same as the first training visit, but this may not be possible due to delay in supplying irrigation equipment. Any delays should be recorded on a deviation log/note to file (CRF 7/8) to allow data analysis to be adjusted accordingly.
(k) Plenty of optimism, encouragement and personal attention.

Visit 2.1:

(l) A telephone call will be made to the patient 14 days (+/- 3 days) after Visit 2 to check everything is proceeding correctly and to resolve any problems (V2.1). If, due to delay obtaining equipment etc, the patient has not started irrigation at this time then the phone call (and other follow up visits) should be re-scheduled for 14 days later, and the reason for this recorded on CRF 7/8.

Visit 2.2:

(m) If there are problems, a further face-to-face session will be offered (V2.2). There is no specific time requirement and will depend on the difficulties encountered and availability of appointments, ideally this visit should be conducted within a week and before visit 3.

Visit 3:

(n) All patients will receive a further training assessment at 2 weeks (+/- 1 week) after Visit 2.1, allowing for any delay as described previously (V3). This visit will be combined with collection of PAC-QOL, PAC-SYM and EQ-5D-5L, EQVAS and should be face to face. The irrigation journal will be reviewed at this visit. A telephone call is an acceptable alternative if this is not possible.
(o) Patients deciding to switch to the alternative system will be trained in the new system by the irrigation nurse and this will be recorded on the note to file, CRF 8 and change/discontinue, CRF12. These patients will not need to complete the questionnaires at 1 month and 3 months if they have already done so.
(p) Standardised guidance on how to tailor therapy to each patient depending on initial response will be provided to specialist nurses/therapists. Changes in regimen as well as system will be documented on the CRF.

Telephone support will be available from the therapist between visits (number given, office hours only). The therapist will complete the intervention CRF at every visit or patient contact. For contact with patients after the training period, a note to file (CRF 8) should be completed, and the patient will also make a note of any contact in their irrigation journal. In the instance of new psychological issues being determined during consultation, referral for psychological support will be deferred until after completion of irrigation training. The exception to this rule would be where there is clinical concern regarding the patients acute mental state requiring more urgent intervention (see withdrawal from treatment criteria). Concerns would be raised by

the irrigation nurse team to the research team, and these would be evaluated by the PI (or a medically-trained deputy) and appropriate action taken. Further follow-up visits (V4-V8) will be conducted by the research team. If the patient requires further input from the irrigation nurse this may be arranged as per local practices. Any contact and any changes made or advice given regarding irrigation should be recorded in the patient journal and irrigation journal.

7.5.2 Switching between anal irrigation systems

After three months of using one system, patients may switch to the other or discontinue therapy and return to routine clinical care. This will be entirely patient-led, and reasons for changing systems will be explored during follow up visits and captured on the CRF. There is therefore no defined protocol for switching treatments as patients may do this for any reason; analysis of time to switching/discontinuing therapy, as well as the patient-reported reasons for doing so, will provide insight into why each irrigation system is or is not successful. In addition, qualitative interviews with patients who have switched or discontinued therapy will be used to explore these issues more deeply (see Section 7.16 below).

7.5.3 INVEST

Radio-physiological investigations

Patients will undergo standardised investigations. If INVEST previously conducted within the last 12 months, results can be carried forward. Pregnancy testing will be conducted as per routine NHS practice (10 day NHS rule) in respect to women between menarche and menopause. Women of equivocal status will have a serum pregnancy test performed as per routine care.

(e) Anorectal manometry using standard or high-resolution methods[40-42], depending on local availability, to determine defined abnormalities of rectoanal pressure gradient during simulated evacuation[43-45].
(f) Balloon sensory testing using standardised methods[46, 47](2ml air per second to maximum 360 ml) to determine volume inflated to first constant sensation, defaecatory desire and maximum tolerated volumes. Rectal hyposensation and hypersensation defined in accord to gender-specific normative data on 91 healthy adults[48]. The rectoanal inhibitory reflex will also be elicited by 50ml rapid inflation (if necessary in 50 mL aliquots up to 150ml).
(g) Fixed volume (50ml) water-filled rectal balloon expulsion test[43,44,49,50]in the seated position on a commode. Abnormal expulsion is defined as abnormal if failure to expel with 1-minute effort for men and 1.5 minutes for women[51].
(h) Whole gut transit study using serial (different shaped) radio-opaque markers over 3 days with single plain radiograph at 120 hours[52,53].

NOTE: INVEST procedures conducted prior to recruitment to the study (i.e. within the past 12 months) may be done using locally available devices and methods.

Treatment

All patients will undergo trans-anal irrigation therapy irrespective of INVEST results, and will be followed up in the same way. The purpose of INVEST in this study is to identify whether certain radio-physiological results correlate with treatment response, i.e. can we predict likelihood of benefitting from irrigation based on pre-treatment investigations. Balloon sensory testing in combination with patient-reported urge to defaecate will be analysed as covariates to determine whether such a relationship is present.

7.6 Concomitant Medications

It is inevitable that patients will seek recourse to laxatives and other dietary supplements during the course of the programme. Experience shows that complete prohibition can lead to unreported laxative use, which might confound findings. Although we will strongly discourage *ad libitum* medication usage and specify a defined breakthrough regimen, we will record co-treatment with sufficient fidelity and integrity to enable use as covariates in analyses using a specific patient journal for this purpose (see standardised outcome framework). A concomitant medications list including a shortlist of contributory or confounding medications will be used to filter on data entry. Patients using one system in the medium/long term may wish to revert to the other system or pause treatment for a short period (for example while going on holiday) for practical reasons. This is permitted but must be recorded in the concomitant medications log. This will not be considered as switching or ending treatments as it is only a short-term measure.

7.7 Criteria for Discontinuation

The interventions proposed are well-established in current clinical practice. There are no defined criteria for discontinuation; however clinicians may withdraw treatment where they have therapeutic or safety concerns, consistent with routine care. Patients may choose to discontinue treatment at any point and return to routine clinical care.

7.8 Procedure for Collecting Data including Case Report Forms (CRFs) and storage

The data collected for the trial will be a mixture of routinely collected data, verifiable against the medical record and patient reported outcome (PRO) or questionnaire data, collected directly to CRF. The following table outlines the data sources, collection requirements and transfer of data.

Study Assessment	**Data Sources**	**Data Transfer**
Brief screening and eligibility criteria check	Patient Interview	CRF1 (OpenClinica)
Informed Consent	Consent Form	none
Structured history including eligibility assessment, demographics, medical history, medications and clinical examination	Patient interview and Medical Notes - routine data	CRF2 (OpenClinica)
Pregnancy Test where applicable	Laboratory Test Result - routine data	CRF2 (OpenClinica)
Baseline Only Assessments (Rome III ConstipationQ & IBSQ, Cleveland ClinicQ, St Marks, joint hypermobility variable)	PROM –Baseline Questionnaire (eCRF/CRF)	Baseline Questionnaire (REDCAP)

Randomisation	Online system	CRF 4
Rectal balloon sensory testing	Medical Notes - routine data	CRF3 (OpenClinica)
Balloon expulsion test	Medical Notes - routine data	CRF3(OpenClinica)
Anal manometry	Medical Notes - routine data	CRF3 (OpenClinica)
Radio-opaque marker transit study	Medical Notes - routine data	CRF3
In therapy assessments (Anal Irrigation)	Medical Notes - routine data PROM - Irrigation Journal	CRF4 (OpenClinica)
Standardised Outcome Assessments - (PAC-QOL,PAC-SYM , , EQ-5D-5L, EQVAS, PHQ9, GAD7, VAS, CC-BRQ, BIPQ-CC)	PROM – Outcome Questionnaires (eCRF/CRF)	Outcome Questionnaire (REDCAP)
Short outcome assessment (PAC-QOL, PAC-SYM, EQ-5D-5L)	PROM – Short Outcome Questionnaire (eCRF/CRF)	Short Outcome Questionnaire (REDCAP)
2 week Patient Diary (bowel)	PROM – 2 week Patient Diary (eCRF/CRF)	Patient Diary (REDCAP)
AE log	Medical Record and PROM	CRF5 (OpenClinica)
ConMed Log	Medical Record and PROM	CRF6 (OpenClinica)
Deviation Log	CRF7	CRF7 (OpenClinica)
Note to File/Contact Log	CRF8	CRF8 (OpenClinica)
Early Withdrawal	Medical Record	CRF9 (OpenClinica)
Study Completion	Medical Record	CRF10 (OpenClinica)
Follow Up – resource use	PROM – Irrigation Journal and Patient Journal	CRF11 (OpenClinica)
Discontinuation/changing therapy	PROM – patient interview	CRF12 (OpenClinica)

Each recruiting site will be required to keep accurate and verifiable source notes in the medical record relevant to each study participant's inclusion and continued participation in the study.

Data will be collected, transferred and stored in accordance with GCP guidelines and data protection requirements. The PCTU SOPs and study data management plan will define the exact process of data collection, transfer and storage and control of study data.

A secure online OpenClinica trial database will be provided by the PCTU to enable remote data entry at sites where this is feasible. This database will provide built in data validation checks with quality control checks performed by checking a predefined percentage of CRF data against data entered into the database. In addition on site monitoring will enable source document verification of records (see section 16).

Patient reported outcome measures (PROMs), including questionnaires and diaries may be collected directly to eCRF using a secure and controlled REDCAP database. An automated email reminder will be sent to participants to remind them to complete the questionnaires and diaries every 12 weeks. Alternatively, participants can complete paper questionnaires and diaries to be entered by the central study team.

All patient identifiable data, such as consent forms, screening and identification logs will be stored in the investigator site files in secure locked cabinets and/or offices, accessible only to delegated members of the study team. Secure methods of data transfer will be used to return CRFs to the coordinating site for centralized data entry, monitoring, quality control and in compliance with GCP. A copy of the CRF held at the site in accordance with GCP.

7.9 Follow-up Procedures

The study duration allows for follow up to a maximum of 12 months with data collection at 3, 6 and 12 months post initiation of therapy. Primary outcome data will be collected at three months. Each participant will have a minimum of 3, 6 and 12 months follow up data for collecting the primary and secondary outcomes. In addition, PAC-SYM, PAC-QOL and EQ-5D-5L, EQVAS will be recorded at the 1-month visit; this is to capture information on early non-responders, and to better understand and characterize this group of patients. Participants will leave the study and return to 'routine clinical care' as determined within their local NHS institution (or be recruited to subsequent trials). Alternatively they may wish to proceed to enrolment in the next work package (Study 3 – Laparascopic Ventral Mesh Rectopexy) within the CapaCiTY programme.

The following data will be collected at each visit up to 12 months:

- Validated symptom and quality of life questionnaires (PAC-SYM and PAC-QOL).Validated generic QOL questionnaires: EQ-5D-5L descriptive system and EQ-VAS[53]. Note: EQ-VAS has a SD of approximately 30 points: a 10% difference in VAS deemed clinically significant can be detected with the large sample sizes proposed.

- Patient Health Questionnaire-9 (PHQ-9) [56-58].
- Generalized anxiety disorder questionnaire (GAD7) [59.]
- Depression, anxiety and somatisation modules of the Patient Health Questionnaire[56-59].illness perception questionnaire[60].
- Global patient satisfaction/improvement score (VAS) and whether they would recommend each treatment experienced to other patients.

- Potentially modifiable cognitive and behavioural psychological variables shown to predict onset and perpetuation of other functional bowel symptoms: negative perfectionism, avoidant and 'all or nothing' behaviour subscales of the behavioural response to illness questionnaire (CC-BRQ), and brief illness perception questionnaire BIPQ (CC).
- A two week patient diary (for 2 weeks prior to each assessment at 3, 6 and 12 months) to record bowel frequency and whether each evacuation was spontaneous (no use of laxatives) and/or complete; patient journal will also capture concurrent medication, health contacts, time away from normal activities (including work). Patients will be contacted by telephone to remind them to start the diary. If patients forget to do this, then it is acceptable for them to start recording the diary on the day they are seen in clinic and for this to be collected two weeks later.
- Resource use data (using patient journals as a prompt and including concomitant medication use).
- Irrigation Diary to record frequency and volume of irrigation and any adverse events.

7.10 Laboratory Assessments

Serum Pregnancy Testing will be performed as per standard care for any women of equivocal status undergoing radiological assessments (INVEST).

7.11 Radiology Assessments

The whole gut transit study usually (90% patients) involves the use of a single plain abdominal radiograph (in 10% patients, a maximum of 2 may be required to image whole abdomen and pelvis). This procedure forms part of routine clinical care for patients with CC at many NHS centres. All practitioners (radiologists, radiographers etc.) directing these studies will hold appropriate IR(ME)R certification.

7.12 Participant withdrawal (including data collection / retention for withdrawn participants)

Individual participants will be able to withdraw from treatment at any time by notifying healthcare professionals involved with the study, and return to routine care without prejudice. Data will be retained for analysis from all participants after the point of consent and recruitment.

Withdrawal from treatment Criteria:

Participant develops any of the following exclusion criteria

- Participant becomes pregnant or intends to become pregnant (only in baseline and intervention phases).
- Participant subsequently diagnosed with proven cause for secondary constipation e.g. Parkinson's disease or bowel obstruction.
- Participant requires new medication with proven effects on bowel function e.g. opioids.

- Participant develops significant intercurrent illness precluding participation.
- Participant requires surgery or other intervention (other than minor ops) during treatment or follow up phase.
- Participant develops acute psychological problem causing safety concern.
- Adverse events secondary to therapy (bleeding, anal fissure, ulceration, pain, bowel perforation) – relative indications for withdrawal depending on the views of the patient and doctor (NB perforation is an absolute indication for withdrawal).
- Elective withdrawal.

Loss to Follow Up (no further interventions or follow up data collected)

- During follow up (up to12 months), participants may be withdrawn from the trial if they become lost to follow up (LTF) after at least 3 failed attempts by research staff to make contact via 2 different methods (e.g. phone and letter).
- Participant chooses to withdraw and does not wish to participate in follow up data collection.
- Death or significant incapacity making follow up data collection impossible.

7.13 Schedule of Assessment (in Diagrammatic Format)

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Assessment	**V0** Pre-Screening	**V1** Screening & Baseline **V1.1: INVEST***	**V2** Intervention assessments	**V2.1 (V2.2**)** Intervention assessments	**V3** 1 month intervention FU review	**V4** 3 month FU visit	**V5** 6 month FU visit	**V6** 12,month FU visit
Minimum Timeframe between visits+ **(Maximum Timeframe)**	**-1 day**	**0**	**+2 weeks** **(+ 8 weeks)**	**+ 2 weeks** **(+/- 3 days)**	**+2 weeks** **(+/- 1 week)**	**+ 2 months** **(+/-1 week)**	**+ 3 months (+/-1 week)**	**+ 6 months** **(+/-1 week)**
Brief screening and providing PIS	x							
Informed Consent		x						
Structured history including eligibility assessment, demographics, medical history, medications, clinical examinations		x						
Pregnancy Test where applicable		x						
Baseline only assessments		x						
Rectal balloon sensory testing*		x						
Balloon expulsion test*		x						
Anal manometry*		x						
Radio-opaque marker transit study*		x						
Randomisation		x						
In therapy assessments (Anal Irrigation)**			x	x	x			

Standardised outcome framework assessments		x				x	x	x
Short Outcome Assessment					x			
Patient Diary Provided		x			x	x	x	
Patient Diary Collected ***			x			x	x	x
Patient Journal Provided		x						
Patient Journal Collected						x	x	x
Irrigation Journal Provided			x		x	x	x	
Irrigation Journal Review					x	x	x	x
Adverse Event and Concomitant Medication Review		x	x	x	x	x	x	x

*V1.1 = INVEST – A minimum timeframe of 2 weeks to allow completion of baseline diary prior to INVEST and maximum of 8 weeks (for logistical purposes).

V2 = commencement of therapy and TAI training; V2.1 = Phone call within 2 weeks

**V2.2 = further training if needed to be conducted prior to or in conjunction with V3 if necessary. V3 = 4 week follow up session (Face-to-face if possible or telephone)

All follow up time points measured from commencement of therapy (V2)

*** Resource use data is collected in patient journal training and retrospective completion of this journal occurs at visit 1.

7.14 End of Study Definition

The end of study is defined as the last patient last visit. The sponsor, REC and local R&D departments will be informed of end of study and site closure and archiving procedures initiated.

7.15 Criteria for Early Termination

If the DMEC, PSC, REC or sponsor determine it is within the best interests of the participants or trial to terminate the study, written notification will be given to the CI. This may be due to, but not limited to; serious safety concerns, serious breaches, acts of fraud, critical findings or persistent non-compliance that negatively affects patient safety or data integrity. If the study is terminated participants will be returned to the NHS normal follow up and routine care.

7.16 Qualitative interviews

The purpose of this qualitative enquiry is to complement the quantitative study of anal irrigation. A phenomenological methodology will be employed and qualitative data will be collected in parallel with the quantitative study. Participants will be recruited separately from the quantitative study, with separate patient information sheets and consent processes.

Sampling

A purposive sample of approximately 35 patients will be invited to interview upon completion of irrigation training and then again at 6 months. Participants do not have to participate in both sets of interviews; a separate set of patients can be interviewed at 6 months. Recruitment can be extended if data saturation is not accomplished by the 35th patient data saturation is defined as the point at which no new or relevant themes emerge. Inclusion and exclusion criteria are as above. Participants will be selected from a sampling grid of potential interviewees to reflect a range of ages, geographical locations, and where possible other pertinent attributes such as ethnicity and gender. An approximately equal number of patients will be selected from each trial arm as follows:

17 patients undergoing low-volume anal irrigation and 18 patients undergoing high-volume irrigation and including those who discontinue early (<3 months), later (3-5 months), those who continue with their allocated treatment, and those who switch. In addition, approximately 10 health professionals involved in delivering the treatment will be interviewed. These healthcare professionals will be evenly distributed across participating centres.

Data Collection

All participants will be told that they might be invited for interview when they are initially informed about the study. Participants will be contacted by a member of the clinical team and if interested in being interviewed a separate PIS will be provided. Participants will be

offered a semi-structured interview in a clinic room or in their own home according to their preference, and will be offered a chaperone to be present if they would prefer. Professionals will be interviewed in a clinic setting. Following written consent, the interviews will be recorded on a digital dictaphone and transcribed into a pseudonymised (alphanumeric code) text document. Interviews will be conducted by the following:

An experienced qualitative researcher working within the wider CapaCiTY research programme, A Clinical Research Fellow at UHND and/or a Health Research Methodologist at Durham University will conduct interviews recruited from the Durham site.

Interviews will explore health professionals' and participants' experiences of recruitment, individual interventions, their training and delivery, and patients' views about outcome measures. A topic guide for each of the interviews and focus groups, informed by the existing literature and our patient advisors, will be developed.

Timing

Patients will be invited to one-to-one interviews on completion of training and will be interviewed a maximum of 4 weeks after training to maximise recall. Patients will be recalled up to 6 months after training and offered an interview. The patients interviewed at baseline do not have to be the same as those interviewed up to six months. Interviews will be conducted throughout to capture relatively early and later experiences and perceptions of the interventions.

Analysis

Interviews will be digitally recorded, anonymised, transcribed verbatim and analysed using a thematic analysis and NVivo8 software (QSR International Ltd, Warrington, UK) for data management. Data analysis will be developed as outlined by Fereday & Muir-Cochrane[61] in the first instance by mapping key concepts derived from the transcripts ('charting') and extracting emergent themes from the transcripts. Prof Norton will co-ordinate and conduct analysis, while for the purposes of Christopher Emmett's MD, independent analysis will be conducted by CE and Dr Helen Close. Emergent themes, together with captured observational data, will form the basis of analytical interpretation. Data will be handled in a confidential manner at all times, and only transferred on encrypted media or via secure electronic transfer.

8. STATISTICAL CONSIDERATIONS

8.1 Sample Size

PAC-QOL is a 28-item disease-specific measure, with each item scored 0-4, and providing an aggregate score 0-4[35]. Superiority of either low volume or high volume anal irrigation is demonstrated by a 10% scale difference (or more), or 0.4, with a variance estimate

conservatively set at SD=1 from the published literature. To detect an effect size of 0.4 (mean/SD =0.4) between the two groups with 90% power and 5% significance at three months requires 133 patients per arm, and 266 total. Allowing for an anticipated 10% loss to follow up (LTFU), then 300 patients will be recruited.

8.2 Method of Analysis

8.2.1 Clinical Outcomes

A full analysis plan will be signed off before allocation codes are made available to the statistician. The codes will not indicate which treatment arm is which so that as far as possible the statistician will remain blind to allocation throughout the analysis. All analyses will be by the intention-to-treat principle. The primary outcome will be PAC-QOL as a continuous variable, analysed at 3-months while the quarantine period is in effect. The proportion of patients continuing with the initial therapy system will be recorded, and the PAC-QOL scores will be analysed using a linear mixed model with a random effect for centre and fixed effects for intervention, trial stratification variables (participants are stratified by sex and females by centre) and baseline PAC-QOL.

Secondary outcomes will be analysed using the principles outlined above for the primary outcome.

Exploratory modelling will be conducted for baseline characteristics: measures of chronic pain, autonomic, joint hypermobility, cognitive, behavioural and mood variables share a common hypothesis that they are detrimental to the success of all treatments i.e. they perpetuate illness in spite of therapy. We will investigate a maximum of 3 interactions between treatment and baseline characteristics. These will be described in the statistical analysis plan *a priori*. Appropriate regression models including interaction terms will be developed to determine the influence of these pre-treatment characteristics on the success of treatments in all work packages.

Life table data for any irrigation will be presented by initial therapy and for specific therapy from date of commencement. Survival analysis will be presented using Kaplan Maier analysis and adjusted using Cox regression. Exploratory analysis will be considered to identify characteristics of sub-groups with greatest persistent benefit from irrigation. These will be described in the statistical analysis plan *a priori*.

Analysis will be performed using proprietary software, (Stata Corp. Texas). $P<0.05$ will be taken to indicate statistical significance. No analyses will be conducted until an analysis plan has been written, reviewed by an independent statistician and signed off.

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Multiple imputation will be considered to address missing covariate values. Details of any imputation to be performed will be described in the statistical analysis plan which will be finalised after initial checks on completeness of the data but before performing any analysis or un-blinding of the data.

8.2.2 Health economic outcomes

The patient journal will facilitate the capture of health economic data which will be recorded on the CRF at each visit. This will be combined with the initial cost of the device and weekly consumables.

Within-trial stochastic analysis will compare the cost/success and cost/QALY of anal irrigation. Patient-level cost-effectiveness analysis will use standard bootstrapping methods to generate cost-effectiveness acceptability curves exploring value-for-money. Within-cohort combined stochastic/probabilistic epidemiological models will be used to assess irrigation and surgery options, exploring relative effectiveness and cost-effectiveness according to patient characteristics.

Cost-effectiveness models that extrapolate beyond 3-6 months duration are problematic in adult constipation, as subsequent care and outcomes are contingent upon subsequent care received and the underlying disease process. However, the programme of work packages, and inclusion of time to failure data capture, provides a unique opportunity to construct probabilistic models exploring optimal pathways from effectiveness and cost-effectiveness perspectives.

Since patients will (within the CapaCiTY programme) be followed along a pathway that includes a series of steps of care, it will be possible to construct costs and outcomes for a range of patient pathways providing comparative longer term cost effectiveness estimates. Patient-level data from recruitment through the various work packages will be used to construct pragmatic, probabilistic models to explore optimal pathways from effectiveness and cost-effectiveness perspectives.

Analyses from NHS and societal perspectives will be supported by recording relevant resource use during each work package, and a common panel of outcomes. Adjustment for time preference will be at the socially accepted rate for cost effectiveness analyses (currently 3.5%/annum for costs and benefits).

8.2.3 Data analysis for MD thesis

The study will form the basis of a thesis for an MD at Durham University by a research fellow (Christopher Emmett) at University Hospital of North Durham (UHND). Patients recruited at

UHND and the Royal Victoria Infirmary, Newcastle-upon-Tyne up to 1st October 2016 (estimated 50 patients) will be analysed in this thesis, including those recruited to the qualitative arm of the study at this site (section 8.17 above). These patients will have a minimum of 3 months of study data. The release of data from the UHND and Newcastle sites for this purpose has been approved by the Chief Investigator on the condition that it may be used for thesis examination but is not published or made publically available until the CapaCiTY programme results are published in full. The qualitative data from the Durham site may be published separately as agreed.

9. ETHICS

9.1 General

This study (Study 2 of the CapaCiTY programme) will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

Ethics approval for the whole CapaCiTY programme (studies 1 to 3) will be sought from one of the London NRECs (exact committee to be determined based on timings and availability). Within the programme, the three studies will however be consented separately as if they were distinct entities. This is necessary to limit patient information which would otherwise be over-burdensome. We have discussed the use of sequential consent forms within one pragmatic enriched design with Dr Art Tucker, national ethics advisor and Chair of the East London and the City REC who confirms this will be practicable.

9.2 Ethical considerations

The protocol has been reviewed by Prof Richard Ashcroft, Professor of Medical Ethics and Law at QMUL. Important considerations that have informed pragmatic design include (a) *limitation of intimate examinations:* to one time point (not repeated if performed before recruitment); (b) *timings of outcomes*: Within this study outcomes will be undertaken at 3 and 6 months from the commencement of the first treatment for all patients, with additional recording of key outcome measures (PAC-QOL, PAC-SYM, EQ-5D-5L, EQ-VAS, Irrigation Journal and Patient journal). For this period of 6 months, patients will not progress to further WPs thus preventing outcome 'contamination'. Additionally there will be a 3 month 'quarantine' from switching irrigation therapy. These delays are akin to that in usual NHS care, during which general supportive care will be provided. This proposed limitations at 3 and 6 months confers no disadvantage and may even represent an acceleration of treatment progression. Ethically, this is viewed as a reasonable trade-off for the commitment to the research programme; (c) *recruitment & consent*: study 2 represents one of the 3 studies incorporated in the NIHR-funded CapaCiTY programme. Although patients may move sequentially through treatments (and therefore studies) during the programme course, study

2 will be consented as a distinct single entity; *(d) qualitative interviews*: these will be in-depth interviews conducted one-on-one (plus a chaperone if requested by the patient) and therefore there are potential risks to the safety of the interviewer. Also, the thorough nature of the interviews could lead to psychological distress for the participant. It is therefore necessary to identify patients who would be at especially high risk in either of these ways and to exclude them from the study. Baseline assessment would identify and enable exclusion of individuals with pre-exiting psychiatric disorders or a history of high-risk behaviours (self-harm, drug and alcohol addiction). Counselling and support from healthcare professionals involved in patient care will be available for any subject experiencing untoward distress.

The investigating team have no conflicts of interest.

10. SAFETY CONSIDERATIONS

Patients recruited who have not had previous INVEST procedures conducted within the last 12 months will undergo a radiological procedure (whole gut transit) using ionising radiation as outlined above. The average dose of this procedure (~0.1mSv) is equivalent to about 2½ weeks annual background radiation dose from living in the UK [NB: this is an approximation which will require re-certification by Barts Health NHS Clinical Physics Dept. based on doses from 20 equivalent procedures]. Further, these investigations would be carried out in routine clinical practice in many centres for patients at the same point as recruitment to this study.

Regarding the intervention, anal irrigation is associated with a very small incidence of bowel perforation, as well as other side effects (bleeding, pain, ulceration, painful haemorrhoids, anal fissure). Patients will be counselled regarding these risks as part of the process of informed consent. In addition, they will be trained in the correct use of the device prior to commencing therapy. All related adverse events and all serious adverse events will be recorded and therapy suspended while these are investigated (see ‘Safety Reporting’ below).

11. DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information related to participants should be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

Identifiable information to be collected from the participants include, full name, DOB and hospital number and contact details at screening. This information will be used to contact participants but will not leave the study site without prior consent and approvals. All case report forms will be pseudonymised. The participant's GP will be informed of their participation in the study.

The trial data will be made available to suitably qualified members of the research team, study monitors and auditors, the sponsor, the REC and regulatory authorities as far as required by law. The participants will not by identifiable with regards to any future publications relating to this study.

11.2 Record Retention and Archiving

When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records (including paper records, digital records and audio files) are kept for a further 20 years. For trials involving BH Trust patients, undertaken by Trust staff, or sponsored by BH or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre.

Each site will be required to archive local site files and patient identifiable information such as consent forms and screening logs for a period of 20 years. At the end of the 20 year retention period, permission should be obtained in writing from the sponsor prior to destruction.

12. LABORATORIES (if applicable)

Serum pregnancy testing will be performed by local NHS biochemistry laboratories.

13. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

13.1 Devices

The following is a list of all devices used. None are specific to the research itself and all are currently used in routine clinical. All are CE marked and approved for use in the UK.

1. Disposable proctoscope (supplier as local NHS practice). This will be commonly be used as part of clinical examination at baseline and is also used to introduce balloon catheters into the rectum during INVEST.
2. High Resolution Anorectal Manometry (HRAM system + Unisensor HRaM catheter (200 uses) and balloons, software, cables, calibration kit, isolation transformer and laptop. Insertion and use are outlined under interventions section [equipment provided at study outset].

3. Standard anorectal manometry catheter, balloons, software, cables, calibration kit and associated equipment; standard equipment in many NHS centres for performing anorectal physiology. Can be used as an alternative where high-resolution manometry is not available (Part of INVEST – see above).
4. Balloon catheters for balloon expulsion test (part of INVEST – see above).
5. Radio-opaque markers for colonic transit study: various suppliers (part of INVEST – see above).
6. Standard departmental X-ray equipment (part of INVEST- see above).
7. Peristeen™ anal irrigation system (Coloplast), Qufora®Balloon/Qufora-Toilet anal irrigation systems (MBH-International): Established anal irrigation systems available on prescription in NHS practice. Other systems with the same mechanism of action may also be used (dependent on local funding and prescribing arrangements).
8. Qufora® Mini anal irrigation system (MBH-International): Established anal irrigation system available on prescription in NHS practice.

All devices are maintained, calibrated and serviced according to standard NHS policies and procedures according to manufacturer's guidance. Training on devices is provided by the supplier's representatives. Additional study SOPs and training will be provided to ensure standardisation across sites, but will be in line with current NHS standard practice.

13.2 Techniques and interventions

There are no experimental techniques within the study. The intervention is outlined in detail above

13.3 Data Collection Tools

The permissions/licenses to use the below instruments have been sought on the understanding sites are permitted to utilise these within this study only, they will be provided to sites as part of the CRF for the study:

- PAC-QOL score: from MAPI Research Trust
- PAC-SYM score: from MAPI Research Trust
- EQ-5D-5L: from EuroQol

The below listed questionnaire-based tools are free to use within the public domain and will be provided to sites as part of the CRFs for the study.

- Depression, anxiety and somatisation modules of the Patient Health Questionnaire.
- Illness perception questionnaire.
- Composite Rome III / Cleveland Clinic constipation questionnaire: free to use.
- Brief, chronic pain, autonomic and joint hypermobility: free to use.
- Negative perfectionism.
- Avoidant and 'all or nothing' behaviour subscales of the behavioural response to illness questionnaire.

13.4 Medicinal product

None

14. SAFETY REPORTING

14.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

Notification and reporting Adverse Events or Reactions

The anal irrigation systems are in widespread and established clinical use throughout the NHS with known adverse event occurring (22%) being mostly low grade and reversible. All trial interventions are as per the standard care provided within the NHS for chronic constipation. Adverse events will be recorded on the CRF. Serious adverse events will be recorded on the CRF and in the medical notes to enable assessment and reporting in line with sponsor and regulatory requirements. Causality will be at the discretion of the health care provider (e.g. research nurse, physiotherapist, principal investigator or delegated member of team). These will be assessed as outlined below.

Trial participants will be advised to seek medical support from their GP for any unrelated signs, symptoms or disease or aggravation of underlying symptoms.

14.2 Serious Adverse Event (SAE)

In other research other than CTIMPs, a serious adverse event (SAE) is defined as an untoward occurrence that:

(a) Results in death.

(b) Is life-threatening.

(c) Requires hospitalisation or prolongation of existing hospitalisation.

(d) Results in persistent or significant disability or incapacity.

(e) Consists of a congenital anomaly or birth defect; or

(f) Is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

14.3 Notification and Reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to NRES website and JRMO SOPs.

Please note in the case of a blinded study, it is recommended the treatment code for the patient is broken in the reporting of an 'unexpected and related' SAE. Please seek advice on how this can be achieved whilst maintaining the team blind. The unblinding of single cases by the PI/CI in the course of a clinical trial should only be performed if necessary for the safety of the trial subject.

14.4 Expected SAEs

The following SAEs are expected to occur rarely in this patient population and will not be reported:

- Hospital admission for exacerbation of constipation symptoms including impaction.
- Hospital admission for unrelated elective surgical procedures or accidental injury.

14.5 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to NRES website and JRMO SOPs.

14.6 Annual Safety Reporting

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor. Please see NRES website and JRMO SOP for further information

14.7 Overview of the Safety Reporting responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

Communication organogram for reporting SAEs

SAE recorded on AE log and followed up until resolution

PI assesses SAE and reports to CI within **24 hours**, PI reports to local institution as per local protocol

CI reports related and unexpected SAE's to PCTU QA manager and Sponsor within **24 hours of PI becoming aware of the event**

CI reports related and unexpected SAE's to MREC within **15 days**

CI reports to DMC every **6-12 months**

CI reports **annually** to MREC

SAEs will be followed up until resolution.

15. MONITORING &AUDITING

The PCTU quality assurance manager will conduct a study risk assessment in collaboration with the CI. Based on the risk assessment, an appropriate study monitoring and auditing plan will be produced according to PCTU SOPs. This monitoring plan will be authorised by the sponsor before implementation. Any changes to the monitoring plan must be agreed by the PCTU QA manager and the sponsor.

> Definition:
> "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities we re-conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits may be conducted by a sponsor's or funder representative.

16. TRIAL COMMITTEES

The project will be under the auspices of the Chief Investigator and the PCTU. The project will be overseen by a Programme Steering Committee (PSC).

The composition and responsibilities of the PSC will comply with the NIHR guidance and PCTU SOP on Trial Oversight Committees. The role of the PSC is to provide overall supervision of the study on behalf of the sponsor and funder to ensure study is conducted in accordance with the principles of Good Clinical Practice (GCP) relevant regulations.

The responsibilities of the PSC will include:

- Ensuring that views of users and carers are taken into consideration.

- Advising on the trial protocol.
- Advising on changes in the protocol based on considerations of feasibility and practicability.
- Assisting in resolving problems brought to it by the PMG.
- Monitoring the progress of the trial and adherence to protocol and milestones.
- Considering new information of relevance from other sources.
- Considering and act on the recommendations of the data monitoring committee (DMC), sponsor and/or MREC.
- Review initial reports and papers for publication.

The PSC will meet to review the protocol before the start of the programme and then soon after the first participants are recruited and either meet or teleconference every 6 months thereafter throughout the lifetime of the programme.

PSC membership includes:

- Programme CI (Knowles)
- Study 1 lead PIs (Emmanuel & Norton)
- Senior statistician (Eldridge)
- Health Economist (Mason)
- Study 2 lead (Yiannakou)
- Joint Study 3 lead (Brown & Lacy Colson)
- An independent chair (Professor John McClaughlin, Professor of Gastroenterology and Nutrition, University of Manchester)
- Programme Manager (Stevens)
- Patient and Public Representatives including (Deborah Gilbert, CE Bowel and Cancer Research and Louise Smalley and Mr Ian McCurrach as patient representative).

Representatives of the trial sponsor and funder will be invited to attend.

A Programme Management Group (PMG) will meet monthly initially during study set up and then less frequently, every 2 months. The PMG will be responsible for day to day project delivery across participating centres, and will report to the PSC. It will include:

- The programme CI (Knowles)
- Study 2 lead PI (Yan Yiannakou)
- Programme Manager (Stevens)
- Member of the INVEST sub-group

- Research nurses
- Research fellows
- Trial Coordinator
- Junior trial statistician
- Data manager
- QA manager

A data monitoring & ethics committee (DMEC) will be convened. The DMEC will meet at least four weeks prior to the PSC to enable recommendations to be fed forward. The DMEC will comprise:

- Independent Chair (Prof David Jayne, Professor of Surgery, University of Leeds)
- An independent medical statistician (Neil Corrigan, Leeds Institute of Clinical Trials Research, University of Leeds)
- Leeds)
- Clinician (Dr Rupert Pearce, Professor & Consultant in Intensive Care Medicine, Royal London Hospital)

A DAMOCLES charter will be adopted, and the project team will provide the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC and follow guidelines set out in the charter.

A constipation research advisory group (CRAG) will be formed as part of a well-developed patient and public involvement (PPI) strategy at QMUL (in close association with the Charity Bowel and Cancer Research). This advisory group will comprise 8 patients and 2 lay members derived from London and Durham. This group will have geographical diversity (North and South) and a disease-appropriate demographic (8 female, 2 male). The CRAG will be involved in;

- Review of participant information sheets, booklets, diaries and advertising/marketing materials.
- Project management by representation on the PSC.
- Parallel qualitative analysis.
- Dissemination of results and lay summaries.
- Presentations at local research events.
- Patient focus groups and workshops.

17. PROJECT MANAGEMENT

17.1 Local Co-ordination

Each participating centre will identify a site specific PI who will nominate a local contact for that centre (this may be him/herself). The PI and local contact will:

- Be familiar with the Trial.
- Liaise with the PCTU and PMG.
- Ensure that all staff involved in the trial are informed about the trial and have received requisite training.
- Ensure that mechanisms for recruitment of eligible participants, including the availability of participant information and data collection tools, are in place; monitor their effectiveness and discuss the reasons for non-recruitment with relevant staff.
- Ensure site staff collect necessary trial data and perform quality checks.
- Notify the CI of any SAE‟s.
- Make data available for verification, audit and inspection processes as necessary, and respond to requests for documentation and data required for centralised monitoring.
- Ensure that the confidentiality of all information about trial participants is respected by all persons.

17.2 Site initiation and training

A central study launch meeting and/or site initiation will be conducted with each site. This will include training in the trial protocol and standard operating procedures, such as data collection, randomisation and taking informed consent. Evidence of appropriate training, local approvals and essential documentation will be required before participants being enrolled at each site. Training will be documented on training logs.

17.3 Project timetable, milestones and projected recruitment

The PMG will be responsible for monitoring adherence to the study timelines and expected recruitment rates. Regular reports will be produced to enable deviations from the project plan to be identified and contingencies planned, discussed and executed in a timely fashion.

A Gantt chart is included in APPENDIX X. Projected recruitment rates are:

01.08.15	First participant
31. 04.16	100 participants
30.11.16	200 participants
30.06.17	300 participants
30.10.17	Last patient intervention
31.04.18	3 month primary endpoint

31.10.18 12 month secondary endpoint

18. FINANCE AND FUNDING

The study is being financed as part of an NIHR PGfAR award RP-PG-0612-20001: £1,971,934. Additional resource will be provided via host CLRNs. The calculation of all costs and contracting has been performed in conjunction with the sponsor.

19. INDEMNITY

Queen Mary University London has agreed to act as study sponsor. Insurance and indemnity will be provided by the sponsor.

20. PUBLICATION POLICY

The Chief Investigator will co-ordinate dissemination of data from this trial. All publications using data from this trial to undertake original analyses will be submitted to the PSC for review before release. To safeguard the scientific integrity of the trial, data will not be presented in public before the main results are published without the prior consent of the PSC. The success of the trial depends on a large number of clinicians. For this reason, credit for the results will not be given to the committees or central organisers, but to all who have collaborated and participated in the trial. Acknowledgement will include all local co-ordinators and collaborators, members of the trial committees, the PCTU and trial staff. All contributors to the trial will be listed at the end of the report, with their contribution to the trial identified. Those responsible for other publications reporting specific aspects of the trial may wish to utilise a different authorship model, such as "[name], [name] and [name] on behalf of the collaborative Group". Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the PSC.

A lay summary of the final results of the trial will be made available for participants on the Bowel and Cancer Research charity website with a link to the full paper.

21. DISSEMINATION OF RESEARCH FINDINGS

Scientific findings will be subjected to international reporting and peer review (targeting appropriate clinical journals e.g. BMJ, Lancet or Gastroenterology). The assimilation of data from this trial with those from other studies and convening of a national CC working group to consider the findings will lead to prototype national guidance that will inform NHS pathway development and commissioning of services. As such, it will be logical to initiate discussions with NICE for the development of a guideline for the management of CC in adults and to

progress adoption by specialist medical and nursing organisations. Although the development of this guidance should naturally facilitate dissemination of the main programme findings to health care planners, policy makers and practitioners, we will also direct this information (and that of individual studies) to the following groups:

1. Study participants and carers: Feedback to all the individual participants, users and carers who have been involved in, or otherwise contributed to, the programme (via a participant newsletter).
2. Charity links and patient groups: results of the studies will be disseminated using the strong web-based and media infrastructure already developed by the Charity Bowel and Cancer Research (B&CR). This infrastructure includes the B&CR website (www.bowelcancerresearch.org which has 2,500 unique web visitors monthly), social media e.g. Facebook site (12,000 followers and), Twitter, and a public relations officer (a free-lance journalist who is employed by B&CR for one day per week who will help develop and edit press releases: 50 local and national news publications in 2012). B&CR is dedicated to breaking down the taboos concerning discussion of bowel problems such as CC. B&CR and several of the applicants have links with other patient organisations and charities e.g. Core, GI Blues, Ileostomy Association and the Bladder and Bowel Foundation.
3. Local health service providers including developing clinical commissioning groups via specially convened local meetings and written reports (led by Janet Sedgewick).
4. The Primary Care Society for Gastroenterology by direct engagement through established connections (Dr James Dalrymple).
5. School children: At an educational level, there are plans for development of an interactive learning tool centred on the theme of embarrassing bowel diseases within the award winning Centre of the Cell, an educational charity based within QMUL and dedicated to inspiring curiosity and learning by connecting science to everyday life (www.centreofthecell.org).
6. NIHR collaboration: The CI is Director of the Barts NIHR HTC for GI disease. Results will be disseminated by the HTC newsletter / website to all UK industrial (n= 90) and clinical partners (25 colorectal centres).

Finally, we will repeat the highly successful 2 day international meeting entitled ‘Current perspectives in chronic constipation’ organised by Dr Scott and hosted by QMUL in February 2009 which was attended by over 250 scientists and clinicians and led to a supplement in the journal Neurogastroenterology & Motility dedicated to CC. This meeting will be planned again for 2019 to coincide with the outputs of the programme.

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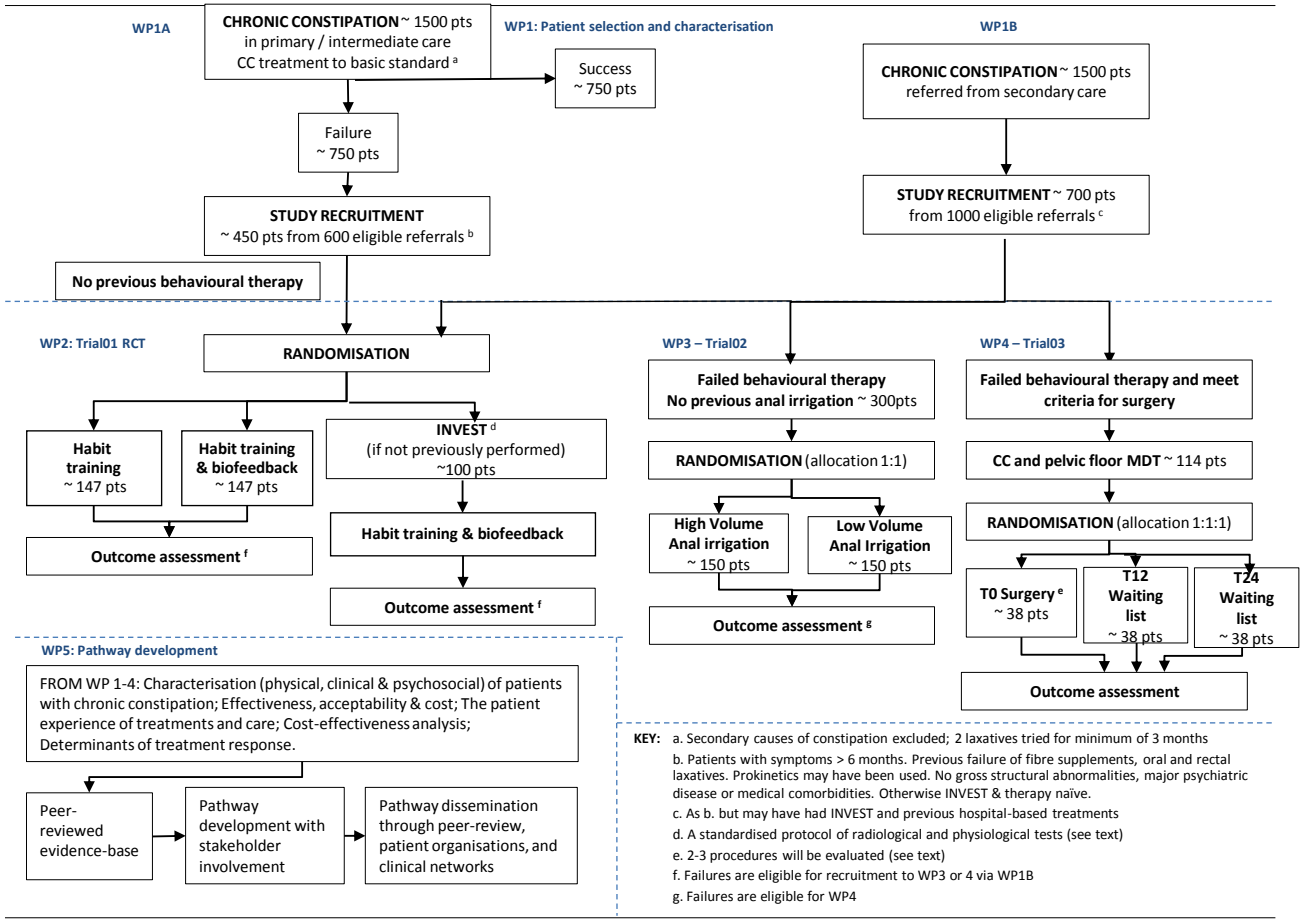
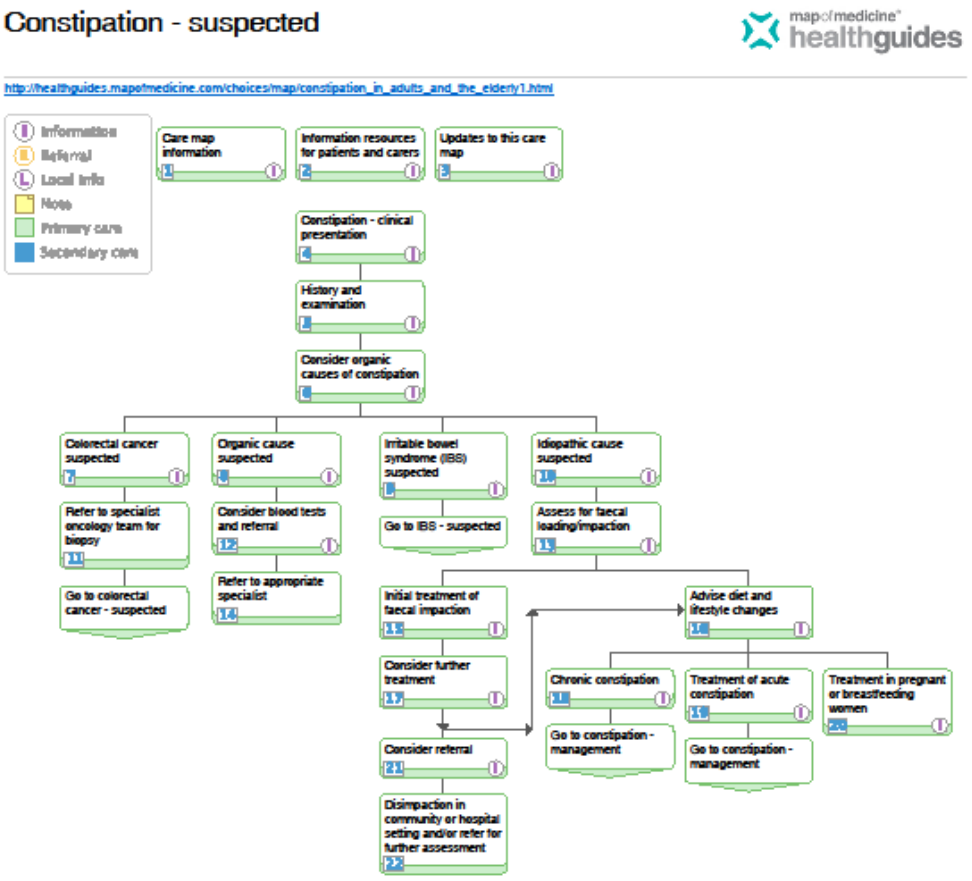
23. APPENDICIES

APPENDIX I – CapaCiTY programme

Fig 1: DESIGN OVERVIEW
with approximate numbers at each stage



APPENDIX II – NHS Map of Medicines



APPENDIX III – Site Codes

NHS Trust	Site Code
Bart's Health NHS Trust [Allison]	BLT
St Marks Hospital at London North West Healthcare NHS Trust [Vaizey]	SMH
University College Hospital London [Emmanuel]	UCL
Guy's and Thomas' NHS Foundation Trust London [Williams]	GST
Sandwell and West Birmingham NHS Trust [Gill]	SWB
County Durham and Darlington NHS Foundation Trust [Yiannakou]	CDD
University Hospital Southampton NHS Foundation Trust [Nugent]	SOT
Norfolk and Norwich University Hospitals NHS Foundation Trust [Speakman]	NNH
University Hospital of South Manchester NHS Foundation Trust [Telford]	USM
University Hospital Leicester NHS Foundation Trust [Miller]	ULH
Sheffield Teaching Hospital NHS Foundation Trust [Brown]	STH
University Hospitals Bristol NHS Foundation Trust [Mabey/Randall]	BRI
North Bristol NHS Foundation Trust [Dixon]	NBT
Newcastle Upon Tyne [Plusa]	NUT
Homerton University Hospital, NHS Foundation Trust [Cuming]	HOM

APPENDIX IV – Study Gantt chart

CapaCITY programme				CHRONIC CONSTIPATION TREATMENT PATHWAY																										
Year			2014			2015						2016						2017						2018						
	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57
Month	March	May	July	Sep	Nov	Jan	Mar	May	Jul	Sept	Nov	Jan	Mar	May	Jul	Sep	Nov	Jan	Mar	May	Jul	Sep	Nov	Jan	Mar	May	Jul	Sep	No
Pre-study																													
Staff Recruitment																													
PROTOCOL DEVELOPMENT																													
Case Report Form Design																													
Database Development																													
PIS/CF design																													
Patient Advertising Materials																													
Randomisation System Set Up																													
Randomisation Request Form																													
Trial SOPs																													
REC Approval																													
Site Feasability Testing/Recruitment																													
Convene PSC/DMC																													
Recruitment Epidemiology Study					01																								
Recruitment Study 2																													
Interventions Study 2																													
Assessments Study 2																									last PEP			last SEP	
Qualitative assessments																													
Milestones / reports																													
Milestones (see text)					I:1/11/14	II:2/1/15			III:01/7/15			IV:28/2/16							V:31/4/17		VI:30/6/1	VII:30/10/17			VIII: 31/4/18				
WP1 data analysis																													
WP2-4 data analysis																													
WP5 data analysis																													
WP5 evidence synthesis																													
WP5 consensus process																													
Reports											I: 30/10/15												II: 30/11/17					III: 30/10/18	
Convene PSC																													
DMC																													
TMG																													

NHS
Health Research Authority

NRES Committee London - City & East

Bristol Research Ethics Committee Centre

Whitefriars
Level 3, Block B
Lewins Mead

Bristol
BS1 2NT

Telephone: 01173421386

06 July 2015

Professor Charles Knowles
Deputy Director National Centre for Bowel Research Surgical Innovation
Queen Mary and Westfield College, University of London
1st Floor, Abernethy Building
2 Newark Street
Whitechapel E12AT

Dear Professor Knowles

Study title: **PRAGMATIC RANDOMISED TRIAL OF LOW VERSUS HIGH VOLUME INITIATED TRANS- ANAL IRRIGATION THERAPY IN ADULTS WITH CHRONIC CONSTIPATION**

REC reference: **15/LO/0732**

IRAS project ID: **172401**

Thank you for your letter responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact

the REC Manager, Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of

the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Advertisement 1]	2	25 November 2014
Copies of advertisement materials for research participants [Advertisement 2]	2.0	25 November 2014
Copies of advertisement materials for research participants [Business Card]	1.0	25 November 2014
Covering letter on headed paper [Covering Letter]		01 April 2015
Covering letter on headed paper [Covering Letter]		25 June 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Verification of Insurance]		29 July 2014
GP/consultant information sheets or letters [GP Letter]	1.0	02 April 2015
Interview schedules or topic guides for participants [Interview Schedule]	2.0	08 January 2015
Letter from funder [Award Confirmation Letter]		21 February 2014
Letter from sponsor [Letter of provisional sponsorship]		02 April 2015
Letters of invitation to participant [Patient Invitation Letter]	1	20 August 2014
Non-validated questionnaire [Patient Journal]		
Non-validated questionnaire [Irrigation Journal]		
Non-validated questionnaire [Patient Diary]	V2	15 June 2015
Non-validated questionnaire [Patient Diary Track Changes]	2.0	15 June 2015
Non-validated questionnaire [Patient Journal]	3.0	12 June 2015
Non-validated questionnaire [Patient Journal Track Changes]	3.0	12 June 2015
Non-validated questionnaire [Irrigation Journal]	3.0	19 June 2015
Non-validated questionnaire [Irrigation Journal Track Changes]	3.0	19 June 2015
Other [GCP certificate Prof Knowles]		21 May 2014
Other [External Trial Oversight Committees]	2.0	03 September 2013
Other [Study Protocol Track Changes]	2.0	22 June 2015

Other [Summary of required REC Changes]		25 June 2015
Participant consent form [Consent Form]	1.0	20 August 2014
Participant consent form [Interview Consent Form]	2.0	08 January 2015
Participant information sheet (PIS) [PIS Main Study]	2.0	22 June 2015
Participant information sheet (PIS) [Participant Information Sheet (PIS) Main Study Track Changes]	2.0	22 June 2015
Participant information sheet (PIS) [PIS Interviews]	2.0	20 January 2015
Participant information sheet (PIS) [PIS Staff Interviews]	2.0	20 January 2015
REC Application Form [REC_Form_30062015]		30 June 2015
Referee's report or other scientific critique report [Peer Review]		05 February 2015
Referee's report or other scientific critique report [Peer Review]		15 February 2015
Referee's report or other scientific critique report [Institute Approval Peer Review]		30 March 2015
Research protocol or project proposal [Study Protocol]	2.0	22 June 2015
Summary CV for Chief Investigator (CI) [CV for CI]		30 July 2014
Summary CV for student [Student CV]		07 April 2015
Summary CV for supervisor (student research) [Professor Yan Yiannakou]		17 July 2014
Validated questionnaire [EQ-5D telephone questionnaire]		
Validated questionnaire [Baseline Assessment Questionnaire]	1.0	13 February 2015
Validated questionnaire [Standard Outcome Assessment Questionnaire]	V2	18 June 2015
Validated questionnaire [Standard Outcome Assessment Questionnaire Track Changes]	2.0	18 June 2015
Validated questionnaire [Short Outcome Assessment Questionnaire]	1.0	13 February 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports

- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0732	**Please quote this number on all correspondence**

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

Yours sincerely

pp Dr John
Keen Chair

Email:nrescommittee.london-cityandeast@nhs.net

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

"After ethical review – guidance for researchers"

Copy to: *Mrs Shiva Taheri, Queen Mary and Westfield College, University of London*

Dr Sally Burtles, Director of Research Services and Business Development

NRES Committee London - City & East

Attendance at Sub-Committee of the REC meeting on 29 June 2015 Committee

Members:

Name	*Profession*	*Present*	*Notes*
Dr Ayse Baxter	Pharmaceutical Physician	Yes	
Dr John Keen	GP (REC Chairman)	Yes	
Dr Dylan Morrissey	Consultant Physiotherapist and Clinical Reader	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mr Rajat Khullar	REC Manager

NHS
Health Research Authority

London - City & East Research Ethics Committee

Bristol Research Ethics Committee Centre

Whitefriars
Level 3, Block B
Lewins Mead

Bristol
BS1 2NT

Tel: 01173421386

24 February 2016

Professor Charles Knowles
Deputy Director National Centre for Bowel Research Surgical Innovation
Queen Mary and Westfield College, University of London
1st Floor, Abernethy Building
2 Newark Street
Whitechapel E12AT

Dear Professor Knowles

Study title: PRAGMATIC RANDOMISED TRIAL OF LOW VERSUS HIGH VOLUME INITIATED TRANS- ANAL IRRIGATION THERAPY IN ADULTS WITH CHRONIC CONSTIPATION

REC reference:	**15/LO/0732**
Amendment number:	**1**
Amendment date:	**28 January 2016**
IRAS project ID:	**172401**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Committee however noted the following points and made suggestions –

The Committee noted that on the e-mail to participants, it is mentioned that the participant is to inform the researcher if questionnaire is not completed prior to the next visit. This applies to the Baseline, Follow Up questionnaires and the baseline diary. It is however not clear how the researcher will be informed. The committee suggested that it would be helpful to add the method in the PIS.

Ms Natasha Stevens provided the revised email document and the Committee was satisfied with the revisions.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Initial Submission Cover Letter]		26 January 2016
GP/consultant information sheets or letters[CapaCiTY Study 2 GP letter]	2	22 January 2016
Letters of invitation to participant [CapaCiTY 2 Patient Invitation Letter]	2	22 January 2016
Notice of Substantial Amendment (non-CTIMP)	1	28 January 2016
Other [Baseline Questionnaire Booklet]	2	22 January 2016
Other [CapaCiTY02 web advertisement]	1	22 January 2016
Other [Emails to participants]	2	18 February 2016
Other [Patient Journal study 2_]	4	22 January 2016
Other [short outcome questionnaires]	2	22 January 2016
Other [Standard outcome questionnaires]	3	22 January 2016
Other [Summary of changes MA-172401]		27 October 2015
Participant consent form [CapaCiTY Consent Form study]	2	22 January 2016
Participant information sheet (PIS) [CapaCiTY02_Participant Information Sheet]	3.0	22 January 2016
Research protocol or project proposal [CapaCiTY02_Protocol]	3	22 January 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0732:	**Please quote this number on all correspondence**

Yours sincerely

pp Dr Ayse Baxter
Alternate Vice Chair

E-mail: nrescommittee.london-cityandeast@nhs.net

Enclosures: *List of names and professions of members who took part in the revie*

Copy to: *Dr Sally Burtles, Barts Health NHS Trust*

Mrs Shiva Taheri, Queen Mary and Westfield College, University of London

London - City & East Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 12 February 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Ayse Baxter	Pharmaceutical Physician	Yes	
Ms Lisa Johnson	CRO	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mr Rajat Khullar	REC Manager

Durham University
School of Medicine, Pharmacy and Health

Shaped by the past, creating the future

Dr David Ekers
Clinical Senior
Lecturer Chair, School of Medicine, Pharmacy and Health
Ethics Sub-Committee

Christopher Emmett
School of Medicine, Pharmacy and
Health Durham University

10th August

2015 Dear

Christopher,

Re: CapaCiTY 02 trial, a multi-centre randomised trial of anal irrigation therapy in chronic constipation

As Chair of the Ethics Sub-Committee, I can confirm Chairs Action approval in relation to the ethics of the above named study. This study been approved by NHS REC (London City and East) and you have confirmed all documentation and procedures will be as per that approval, therefore re- application to the SPMH Ethics Sub-Committee for full ethical review is not required.

The governance arrangements of the study being delivered through Durham University sites and insurance cover should be confirmed with Andrew Watt and the Research Office.

Good luck with your study and please contact me if you require any further

information. Kind regards,

David Ekers

Durham University
School of Medicine, Pharmacy and Health

Shaped by the past, creating the future

Dr David Ekers
Clinical Senior
Lecturer Chair, School of Medicine, Pharmacy and Health
Ethics Sub-Committee

Christopher Emmett
School of Medicine, Pharmacy and
Health Durham University

10th August

2015 Dear

Christopher,

Re: CapaCiTY 02 trial, a multi-centre randomised trial of anal irrigation therapy in chronic constipation

As Chair of the Ethics Sub-Committee, I can confirm Chairs Action approval in relation to the ethics of the above named study. This study been approved by NHS REC (London City and East) and you have confirmed all documentation and procedures will be as per that approval, therefore re- pplication to the SPMH Ethics Sub-Committee for full ethical review is not required.

The governance arrangements of the study being delivered through Durham University sites and insurance cover should be confirmed with Andrew Watt and the Research Office.

Good luck with your study and please contact me if you require any further

information. Kind regards,

David Ekers

Appendix II: Patient Information Sheets and Consent forms

- **Patient Information Sheet CapaCiTY 02 Quantitative Study**
- **Consent Form CapaCiTY 02 Quantitative Study**
- **Patient Information Sheet CapaCiTY 02 Qualitative Study**
- **Consent Form CapaCiTY 02 Qualitative Study**

[insert trust logo]

Did you know, 1 in 10 people suffer from chronic constipation? To find out more about current treatments we are studying, please read this information sheet.

Participant Information Sheet

Study Title: **Chronic Constipation Treatment Pathway, Study 02**

Lay Title: **Low volume versus high volume anal irrigation therapy for the treatment of adults with chronic constipation**

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. One of our team will go through the information sheet with you and answer any questions you have. We would suggest this should take about 15 minutes. We will give you at least a day to make your decision, but you can take as much time as you like. Talk to others about the study if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear.

Part 1: About the research

What is the purpose of the study?

Constipation is a common condition that most people will suffer with at some point in their life. In some people the symptoms can become chronic and severely affect their day to day activities. Chronic constipation is described as someone having

symptoms that last for over 6 months and has not responded to simple lifestyle changes and laxatives.

The condition can be very difficult to treat even in specialist centres. The treatments available include laxatives, newer drugs, specialist led bowel retraining programmes, anal irrigation and surgery. There are also specialised investigations that can be carried out to see if an underlying cause can be found (these are described under visit 1.1). However, the benefits of these tests are still unclear.

The main aim of this study is to assess how effective anal irrigation therapy is in treating chronic constipation in people who have not been helped by specialist-led bowel retraining therapy. Anal irrigation involves putting water into the bottom to stimulate a bowel motion. There are two main systems used to perform anal irrigation and they are slightly different. However, we do not know which one is the better treatment or if in fact they have a similar effect. One system uses a smaller amount of water (low-volume system) and the other uses a higher volume of water (high-volume system). The study will look at how well the symptoms of chronic constipation improve with each of these systems. We will also use specialist tests to investigate the underlying causes of constipation (such as bowel obstructions or blockages), and see if the high volume system is

better than the low volume system in certain patients. This may be helpful for clinicians when deciding whether to prescribe one system over the other. In addition, the cost effectiveness to the NHS will be assessed.

The low volume system consists of a small pump attached to a disposable cone. This is used to insert a small amount (70ml) of lukewarm tap water into the bottom, and this can be repeated as needed.

The high-volume system consists of a bag attached to a tube which is passed into the back passage and held there either by hand or with an inflatable balloon. A larger volume (up to 1.5 litres) of water can be inserted using this technique.

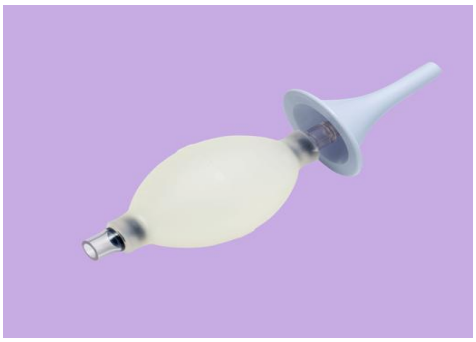


Figure. 1: Low volume irrigation system

Fig

Why have I been invited?

You have been asked to take part in this study because you are between the age of 18-70 and have symptoms of chronic constipation. You have also undergone specialist-led bowel re-training (such as habit training and/or bio-feedback) without improvement of your symptoms. Your doctor or specialist nurse have decided anal irrigation would be the next suitable treatment option for you. This research is taking place at approximately ten NHS practices across the UK and this study will be one of three interlinked studies for chronic constipation taking place over 5 years. You may be asked if you wish to participate in more than one study.

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide to join the study. We will describe the study and take you through this information sheet. If you agree to take part, we will then ask you

to sign a consent form. You are free to withdraw at any time without giving a reason. If you decide not to participate, or withdraw at any time, the standard of care you receive will not be affected.

What will happen to me if I take part?

The anal irrigation therapy you receive will be no different to that already offered on the NHS. However, you and your doctor will not be able to choose which irrigation system you will use. You will be asked to complete a number of questionnaires, diaries and journals to help researchers assess the effectiveness and cost effectiveness of the treatment.

Your participation in this particular study will last for up to 12 months and will involve up to 6 visits to the hospital (please see diagram below). Each visit will take up to an hour. This study is a randomised trial, which means we put people into 2 different groups and start each group on a different treatment. The results are then compared to see if one treatment is better than the other. To try to make sure the groups are the same to start with, each patient is put into a treatment group by chance (randomly). This is because sometimes we don't know which way of treating patients is best. Patients have a fifty-fifty chance of going to each of the groups. You need to continue with this therapy for three months, at which point you will answer a series of questionnaires to help us assess whether this has been an effective treatment for you. These questionnaires only take 10-20 minutes to complete.

Visit 1: Initially you will have a medical history taken and undergo a physical examination including a brief examination of your back passage (if not already performed in the last 3 months). Women of childbearing potential will be asked to take a urine pregnancy test and use effective contraception whilst in the study. You will be asked to complete quality of life questionnaires. A 2 week bowel diary will be given to complete at home, this should take only a couple of minutes at the end of each day. You will also receive a 'patient journal' to record information about your medications and visits with healthcare professionals for your constipation. You will keep this journal throughout your involvement in the study and this information will be reviewed at each follow-up visit. You have the option to complete all quality of life questionnaires and the diaries either on paper or on a secure online database, using any handheld device or computer. If you complete your assessments online, your email address will be shared with the coordinating centre, Queen Mary University, and you will receive an automated email reminder and a link to complete your online assessments.

Visit 1.1: Specialist Gastrointestinal (GI) Physiological Investigations

You will then undergo a number of more precise tests looking at the structure of the lower bowel and back passage and how it works and any abnormalities (these will not be repeated if performed within the last 12 months). This may require 1-2 additional visits to the hospital and waiting times of approximately 4 weeks, which is the normal NHS waiting time for these tests.

1. Anorectal manometry with sensory testing– This includes insertion of a balloon catheter (see figure 3) into the back passage to measure sensation and contractions and also your ability to push out the balloon.

2. Gut transit study – Measures the movement of food through the stomach and intestines. This requires you to swallow 3 gel capsules (size of a normal antibiotic capsule) filled with markers that will show up on an X-ray. The markers look like white spots or rings in the X-ray pictures, taken 120 hours after swallowing the capsules. You will be required to stop taking laxatives before having this test.

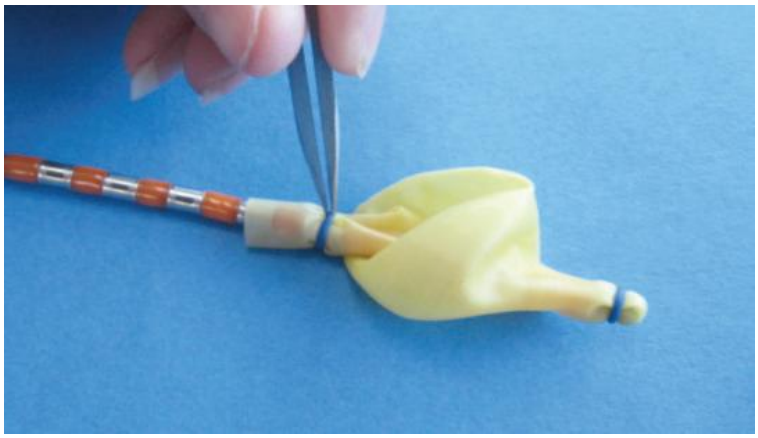


Figure 3: Balloon catheter for investigations

One of these tests includes an X-ray with a very small dose of radiation equivalent to about 2½ weeks annual background radiation dose from living in the UK. As there will be use of X-rays, it is very important to let the research team know if there is any likelihood that you are pregnant. For this reason you may be asked to perform a pregnancy test and will be excluded from the study if you are pregnant or trying to get pregnant. Women entering the study will also be asked to use proven methods to prevent pregnancy throughout the course of the study. Women must advise the research team if they become pregnant or would like to start trying to become pregnant. If this happens you will be withdrawn from the study treatment but may continue to complete diaries and questionnaires if you like.

Visit 2: You will be trained by a nurse to use the anal irrigation system you have been randomly assigned to during a face-to-face visit lasting approximately 45 minutes to 1 hour. You will then begin to use the treatment as directed at home. You will also be asked to keep an irrigation journal to describe how many times you use anal irrigation each week and if you have needed more or less water. This journal will also record any side effects. You will continue to keep the journal until the end of the study, it should only take you a couple of minutes each week to complete. One of the team will contact you after two weeks by telephone so that any problems can be addressed. If you require a further observed training visit then this will be arranged at this time. Your 2 week patient diary provided at visit 1 will be reviewed at this visit.

Visit 3: You will then be seen at the clinic 4 weeks after starting treatment to see how you are getting on. You will be asked to complete a short set of questionnaires and your irrigation journal will be reviewed at this point.

Visit 4-6: You will then be followed up initially 3 months after starting treatment, then after 6 months and then12 months. At these follow up visits you will be asked to complete further quality of life questionnaires, and return your bowel diary, patient journal and irrigation journal. If you need to see the irrigation nurse for advice during this time then this is permitted. You will be asked to record any contact with irrigation nurses, along with advice given and changes to your irrigation regime, in the irrigation journal.

Switching Anal Irrigation Systems

After 3 months if the irrigation system you were assigned to is not working, you can switch to the other system to see if that works better for you. We will record the date on which you stopped one irrigation system and started the other, as well as your reasons for doing so. If you do decide to switch treatments then you will need another training visit to learn how to use the new system. You will also be contacted after about 7-14 days of starting the new treatment and again at 4 weeks. You will not be asked to repeat the questionnaires and diaries.

Allowed Rescue Medications

If you are having severe symptoms despite your irrigation treatment, you will be advised which laxative medications you may take to alleviate this. These will include several laxatives available on prescription (Bisacodyl, Movicol, Lactulose) as well as glycerine suppositories. You will then continue to have regular follow up visits.

What will I have to do?

If you choose to be part of this study, it is important for you to:

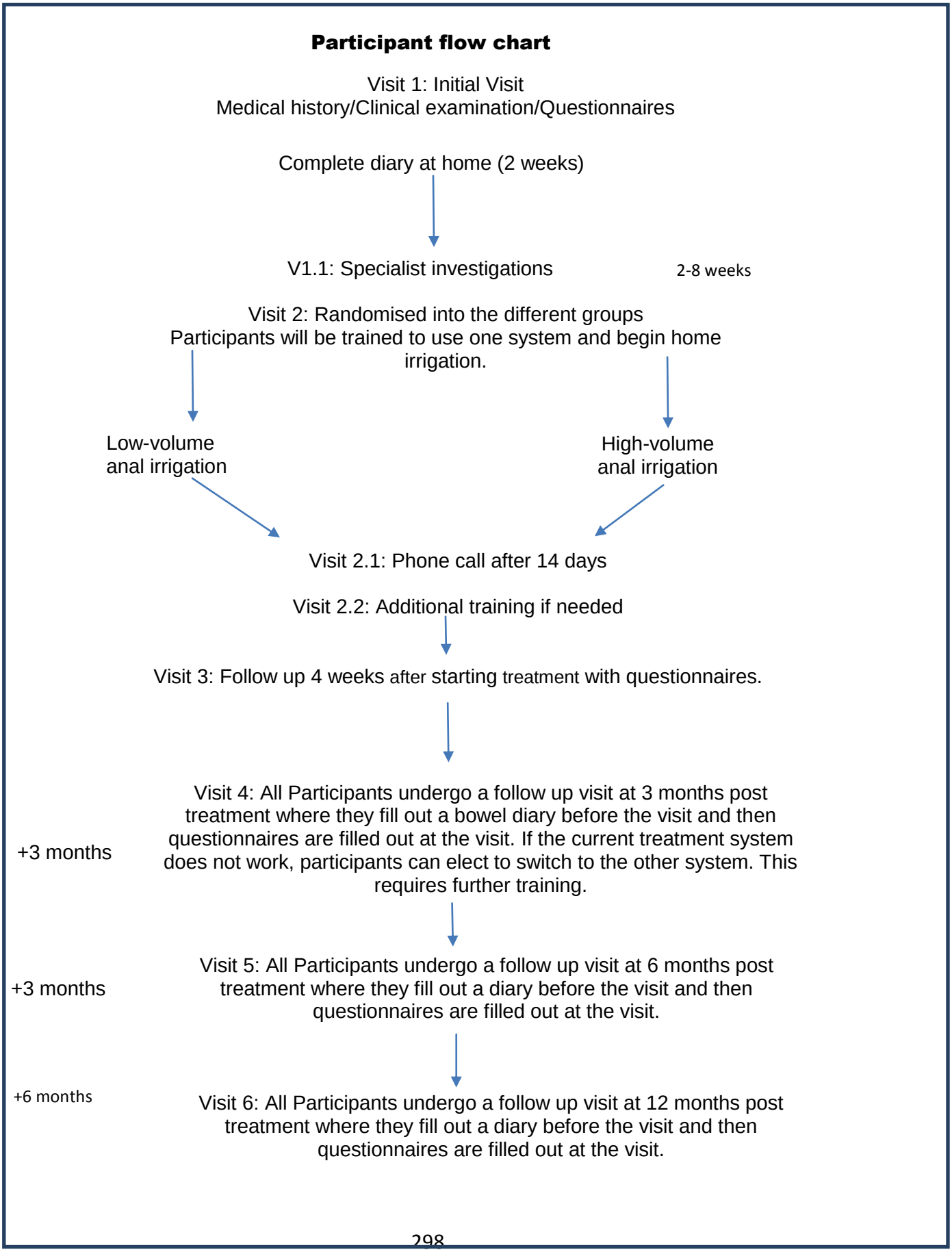
- Discontinue other therapies apart from the anal irrigation and the defined 'rescue' therapies.
- Attend your visits on the scheduled dates.
- Complete your diaries, journals and questionnaires.
- Follow the instructions you receive during the visits.
- You should check with the researcher of this study before joining in any other research trials.
- Women of child-bearing potential should use proven method of contraception throughout the course of the study.

You may also be approached to take part in one to one interviews. This is up to you to decide separately to this part of the study. If you are interested, your contact details will be used to give you further information and you will be consented to take part at a later date

Expenses and Payments

If you decide to take part you will be reimbursed for your expenses incurred with the extra visits to the hospital. This will be £60 given out over the course of the study e.g. £20 each after completion of visit 2, visit 5, and visit 6.

Participant flow chart



What are the possible disadvantages, risks and side effects of taking part?

The study involves procedures that are done routinely in normal care and have been done daily in specialist centres for a long time. One of the routine tests uses X-rays. We are all exposed daily to 'Background Radiation' that comes from natural sources all around us. The X-rays you could receive during the test are equal to about 2½ weeks annual background radiation and considered minimal risk.

The possible side effects of anal irrigation include pain, bleeding, painful haemorrhoids and anal fissure. Some minor discomfort can be experienced, including leakage of water or leakage of stool post-irrigation. You may experience some sort of technical issue with using equipment (for example burst balloon). Approximately a quarter of patients experience some form of minor side effect but these are often well tolerated and reverse by themselves upon stopping irrigation. The only serious risk is of perforation (making a hole in the bowel). This however has only been described in a tiny proportion (less than 1 in 10 000) of patients.

What are the possible benefits of taking part?

We cannot promise the study will help your constipation but you will receive treatments which are considered the routine therapy at the current time. In addition the information we get from this study will help inform future treatment options for people with chronic constipation.

What happens when the research study stops?

If you require further treatment you will return to being looked after in the regular NHS clinic.

What if there is a problem?

Any complaint about the way you have been dealt with during the clinical trial or any possible harm you might suffer will be addressed. The detailed information concerning this is given in Part 2 of this information sheet.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

If new information becomes available about the treatments being studied or the way in which we are planning to conduct the study, you will be notified so that you have an opportunity to re-consider your involvement. This is very unlikely to occur but if it does the researcher will discuss this with you and ask you to sign a document confirming the changes were explained and you have agreed to either continue or withdraw and return to routine care.

What will happen if I don't want to carry on with the study?

You are free to drop out of this study at any time by notifying the study doctor and without having to give a reason. This would not affect the care you receive. If you withdraw from the study any information collected up to that point will still be used but no further information will be collected. You may also be given the option to withdraw from treatment but continue to complete questionnaires and diaries if you wish.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Please insert local investigator contact details here). If you remain unhappy and wish to complain you should contact the Patient Advice and Liaison Service (PALS) <insert local Pals contact here>

We do not expect you to suffer any harm or injury as a result of this research. Anal irrigation is relatively low risk with rare, minor and reversible side effects as explained in the risks section of part 1. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action against the sponsor Queen Mary University of London, but you may have to pay your legal costs.

Will my taking part in this study be kept confidential?

If you consent to take part in this study, doctors, nurses and other personnel involved in the study may need access to your medical records and test results. The records obtained while you are in this study will remain strictly confidential at all times. The information will be held securely on paper and electronically under the provisions of the 1998 Data Protection Act. Your relevant data will not be passed to anyone else outside the research team or the Sponsor, who is not involved in the trial. You will be allocated a unique participant number, consisting of the study

number, a hospital code and a number given in order of enrolment. This code will be used to identify you on all trial forms. Your identifiable records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. Your email address and/or phone number may be shared with the coordinating centre at Queen Mary University and Kings College University in order to arrange your follow up assessments and/or interviews. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 20 years. Arrangements for confidential destruction will then be made.

Will my GP be informed of my involvement?

Your GP, and other doctors who may be treating you, will be notified that you are taking part in this study.

What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor after the study has ended. The results will also be published at the end of the study on the bowel and cancer website at www.bowelcancerresearch.org

Who is organising and funding the research?

The sponsor, who is responsible overall for this study is Queen Mary University of London. The research is being funded by the Department of Health through the National Institute for Health Research (NIHR).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your safety, rights and wellbeing. This study has been reviewed and approved by London City and East Research Ethics Committee.

Further information and contact details

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the procedures involved.

Principle Investigator

Name *add name* Tel. Number: *add Tel. number*

Your Research/Specialist Nurse/Research Fellow *delete as appropriate*

Name *add name* Tel. Number: *add Tel. number*

STUDY CONSENT FORM

Title of Project: **Chronic Constipation Treatment Pathway, Study 02**

Name of Researcher: **Professor Yan Yiannakou, professor of Neurogastroenterology**

County Durham and Darlington NHS Foundation Trust

(Yan.yiannakou@nhs.net. Tel: 07584387147)

Study ID: ☐☐ - ☐☐☐ - ☐☐☐☐

	Place initials in each box
1. I confirm that I have read and understand the Patient Information Sheet dated **22 Jan 2016** (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Queen Mary, University of London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to undergo GI Physiological tests including tests using X-rays.	
5. I agree for my contact details to be passed to study interviewers so I can be contacted about taking part in one to one interviews	
6. I agree to my GP being informed of my participation in the study.	
7. I agree to take part in the above study.	

Print Name of Participant	*Date*	*Participant's Signature*
Print Name of person taking consent	*Date*	*Signature of person taking consent*

[insert Trust logo]

Participant Information Sheet

Study Title: **Chronic Constipation Treatment Pathway, Patient Interview Study 02**

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. One of our team will go through the information sheet with you and answer any questions you have. We'd suggest this should take about 15 minutes. We will give you at least a day to make your decision, but you can take as much time as you like. Talk to others about the study if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Ask us if there is anything that is not clear.

Part 1: About the research

What is the purpose of the study?

The Capacity-2study compares two systems of trans-anal irrigation (TAI) treatment for chronic constipation. This part of the study uses interviews to ask participants about their experiences of the different systems of transanal irrigation, and whether they feel their constipation has improved or not. This will help to improve how chronic constipation is treated in the future.

Why have I been invited?

You are currently taking part in CapaCiTY study 2 where you are undergoing trans-anal irrigation therapy with one of two different systems. You have told us that you were willing to be interviewed.

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time without giving a reason, even after you have agreed to take part. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part you will be interviewed by a researchereither at your home or in the clinic where you are being treated, whichever is better for you. The researcher has a lot of experience of working with people with bowel problems, including those with chronic constipation, and will help you talk about the treatment you have received or are receiving and your suggestions for changing or improving the treatment. You will be able to talk about your feelings in a way that makes you feel comfortable. The interview will take no more than an hour and will be recorded on a digital voice recorder. The interview will be typed out by a professional transcriber and the audio file will then be deleted.

What are the possible benefits or risks of taking part?

By sharing your experiences with us you could help a great many other people with chronic constipation. What we learn from you will help in the development of future treatments.

Talking about tough issues can be hard for people. We know that it can help a lot to be able to talk freely with someone who is keen to hear what you want to say and will not judge you in anyway. As we are talking about a very personal subject there is a risk that you will find it upsetting. The researchers you will be talking to are experienced in talking to patients.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2. The professional who will transcribe your interview is also bound by a code of conduct to keep your information confidential.

This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the study?

You are free to drop out of this study at any time by notifying the study doctor and without having to give a reason. This would not affect the care you receive. If you withdraw from the study any information collected up to that point will still be used but no further information will be collected.If you become unable to complete the study you will be withdrawn but the data collected up until then will still be used.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Please insert interviewer contact details here). If you remain unhappy and wish to complain you should contact the Patient Advice and Liaison Service (PALS) <insert local Pals contact here>

Will my taking part in this study be kept confidential?

The information will be held securely on paper and electronically under the requirements of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or to the Sponsor, who is not involved in the trial. You will have already been allocated a unique participant number, consisting of study numbergiven in order of enrolment. This code will be used to identify you. Before anything is published, all information that could identify you, for example, names and places,will be taken out.

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 20 years. Arrangements for confidential destruction will then be made.

Will my GP be informed of my involvement?

Your GP will not need to be informed about your participation in this part of the study.

What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none

of the participants involved in the trial will be identified in any report or publication.We will not refer to you by name in the published information.

Should you wish to see the results, or the publication, please ask your interviewer or a member of the research team (see contact details at the end). The results will also be published at the end of the study on the bowel and cancer website at www.bowelcancerresearch.org

Who is organising and funding the research?

The sponsor, who is responsible overall for this study is Queen Mary University of London. The research is being funded by the Department of Healththrough the National Institute for Health Research (NIHR).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your safety, rights and wellbeing. This study has been reviewed and approved by London City and East Research Ethics Committee.

Further information and contact details

You are encouraged to ask any questions you wish, before, during or after your treatment. If you require any further information or have any concerns while taking part in the study please contact one of the following people:

YourInterviewer

Name *add name* Tel. Number: *add Tel. number*

Your local investigator

Name *add name* Tel. Number: *add Tel. number*

Patient Advice and Liaison Service (PALS) Please add local PALS contact details here

INTERVIEW CONSENT FORM

Title of Project: **Chronic Constipation Treatment Pathway, Study 02**

Name of Researcher: **Professor Yan Yiannakou, Professor of Neurogastroenterology, County Durham and Darlington NHS Foundation Trust**

(Yan.yiannakou@nhs.net. Tel: 07584387147)

Study ID: ☐☐ - ☐☐☐ - ☐☐☐☐

	Place initials in each box
8. I confirm that I have read and understand the Information Sheet dated **20 January 2015** (version **2**) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
9. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
10. I agree to take part in a 60 minute interview and I understand that this will be audio taped and transcribed.	
11. I agree to take part in the above study.	

Print Name of Participant	*Date*	*Participant's Signature*
Print Name of person taking consent	*Date*	*Signature of person taking consent*

Appendix III: Publications

- **Trans-anal irrigation therapy to treat adult chronic functional constipation: Systematic review and meta-analysis.** Emmett C, Close H, Yiannakou Y, Mason J; BMC Gastroenterology (2015)15:139. DOI 10.1186/s12876-015-0354-7
- **Low-volume versus high-volume initiated trans-anal irrigation therapy in adults with chronic constipation: study protocol for a randomised controlled trial.** Emmet C, Close H, Mason J, Taheri S, Stevens N, Eldridge S, Norton C, Knowles C, Yiannakou Y; BMC Trials (2017) 18:151 DOI 10.1186/s13063-017-1882-y

Emmett *et al. BMC Gastroenterology* (2015) 15:139

DOI 10.1186/s12876-015-0354-7

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Trans-anal irrigation therapy to treat adult chronic functional constipation: systematic review and meta-analysis

Christopher D. Emmett[1*], Helen J. Close[2], Yan Yiannakou[3] and James M. Mason[2]

Abstract

Background: Trans-anal irrigation (TAI) is used widely to treat bowel dysfunction, although evidence for its use in adult chronic functional constipation remains unclear. Long-term outcome data are lacking, and the effectiveness of therapy in this patient group is not definitively known.

Methods: Evidence for effectiveness and safety was reviewed and the quality of studies was assessed. Primary research articles of patients with chronic functional constipation, treated with TAI as outpatients and published in English in indexed journals were eligible. Searching included major bibliographical databases and search terms: bowel dysfunction, defecation, constipation and irrigation. Fixed- and random-effect meta-analyses were performed.

Results: Seven eligible uncontrolled studies, including 254 patients, of retrospective or prospective design were identified. The definition of treatment response varied and was investigator-determined. The fixed-effect pooled response rate (the proportion of patients with a positive outcome based on investigator-reported response for each study) was

50.4 % (95 % CI: 44.3–56.5 %) but featured substantial heterogeneity (I^2 = 67.1 %). A random-effects estimate was similar:

50.9 % (95 % CI: 39.4–62.3 %). Adverse events were inconsistently reported but were commonplace and minor.

Background

Overview of the condition

Chronic constipation may be defined as 'a symptom-based disorder defined as unsatisfactory defecation characterised by infrequent stools, difficult stool passage, or both, for at least three months' [1]. For the purposes of this review, 'chronic functional constipation' refers to any condition fitting broadly within this definition, with no clear under- lying cause. This includes obstructed defecation syndrome (ODS), functional defecation disorder (FDD), chronic idio- pathic constipation (CIC), and constipation-predominant irritable bowel syndrome (IBS-C). This reflects the consid- erable overlap in symptoms between each of these condi- tions [2], and also the fact that observational studies indicate many patients reporting constipation do not fulfil the Rome III criteria for chronic functional constipation [1]. This definition does not include constipation sec- ondary to a neurological cause (for example, spinal cord injury, stroke, Parkinson's disease, Multiple Sclerosis), opioid-induced constipation or constipation secondary to any other medical diagnosis.

Chronic constipation is a common condition in the com- munity: a recent systematic review [3] gave a pooled preva- lence of 14 %, although it becomes more common in older people and women. There is a considerable burden of symptoms and decreased quality of life [1]: one recent study reporting 'extremely/very bothersome' symptoms in 72 % of IBS-C patients, 62 % of CIC patients with abdom- inal symptoms and 40 % of CIC patients without abdominal symptoms [2]. The costs of treating constipation are sig- nificant and appear to be increasing; one American study reported aggregate national (U.S.) costs of Emergency Department attendances due to constipation of $1.6 billion in 2011 [4].

* Correspondence: Christopher.Emmett@nhs.net
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Full list of author information is available at the end of the article

Trans-anal irrigation

Trans-anal irrigation therapy (TAI) is in widespread use throughout the UK as a treatment for bowel dysfunction. Irrigation involves instilling tap water into the rectum via the anus, using either a balloon catheter or cone de- livery system. This is attached via a plastic tube to an ir- rigation bag holding up to 2 l of water; alternatively a low-volume system consisting of a hand pump and a cone may be employed. Low-volume systems deliver ap- proximately 70 ml per irrigation; high-volume systems deliver up to 2 l of irrigation, although typically only 0.5–1.5 l is required. Patients vary in the frequency and volume of irrigation depending on their response to treatment; typically, irrigation is used 2–3 times per week. The low-volume system is cheaper, costing ap- proximately £750 p.a. based on alternate-day use, com- pared with approximately £1400–1900 for high-volume irrigation, and may be more acceptable to patients. It is not known which system is more effective.

Irrigation has been used successfully to treat adults and children with neurogenic constipation [5–7], and faecal incontinence [8]. Proposed mechanisms of action include simple mechanical washout, colonic movement stimulated by the washout, or a combination of these [8]. However, evidence for the use of trans-anal irriga- tion therapy for chronic functional constipation in adults is not

universally acknowledged, and there are questions about long-term benefit [9].

A review of current evidence for irrigation was under- taken to define what is known about this treatment as well as to identify areas where evidence is lacking and further research is required.

Research question

What is the strength of the evidence for trans- anal irri- gation therapy for chronic functional constipation, with reference to effectiveness, safety and methodological quality of studies?

Methods

Eligibility criteria

Primary research articles that include patients with chronic functional constipation as defined above, treated with retrograde trans- anal irrigation at home as outpa- tients, and published in English in indexed journals were eligible. The following were not eligible for inclusion: arti- cles solely studying patients with a known cause for their constipation (e.g., neurogenic constipation, opioid-induced constipation, other organic cause); conference abstracts, audits, letters and commentaries; articles studying ante- grade irrigation (Table 1). Reviews were not included but relevant review articles [8, 10] were screened for further relevant studies, as were citations of retrieved studies. No protocol was registered, however the review was reported in accordance with the PRISMA statement (2009) [11].

Search strategy

The following databases were systematically searched through Ovid Online:

- "All EBM Reviews" (comprising: Cochrane Database of Systematic Reviews (2005 to March 2015), ACP Journal Club (1991 to March 2015), Database of Abstracts of Reviews of Effects (1st Quarter 2015), Cochrane Central Register of Controlled Trials (March 2015), Cochrane Methodology Register (3rd Quarter 2012), Health Technology Assessment (1st Quarter 2015), NHS Economic Evaluation Database (1st Quarter 2015));
- Embase (1974–2015 Week 15);
- Ovid MEDLINE(R) (1946–April Week 2 2015).

The following search terms were used (searched in 'all fields'): "bowel dysfunction"; "defaecation."; "defecation"; "constipation"; "irrigation". The Boolean Operators "AND" and "OR" were used to combine these terms appropriately and refine the search (Table 2). The search was limited to English language articles and to studies in humans.

Abstracts and citations were screened by one re- searcher (CDE) and potentially relevant articles were

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
Primary research	Audit/letters/commentaries/opinion/review articles
Patients with Chronic Functional Constipation (Obstructive defaecation and/or slow transit/IBS-C)	Studies in children (<18 years) only
Full articles published in peer-reviewed journals	Studies in neurogenic constipation only
English Language	Studies where all patients have undergone colorectal surgery (resection or rectopexy, etc.)
Retrograde irrigation using standard equipment performed at home	Studies in stoma patients only
Primary outcome is patient symptom improvement/response to treatment	Studies in antegrade irrigation only

Table 2 Search of bibliographic databases

Number	Searches	Results
1	Constipation.af[a]	90438
2	Bowel dysfunction.af	2264
3	Defecation.af	25606
4	Defaecation.af	1921
5	Irrigation.af	55773
6	1 OR 2 OR 3 OR 4	110886
7	5 AND 6	517
8	Limit 7 to English language	452
9	Limit 8 to Humans	405
10	Remove Duplicates from 9	292

[a]*af* all fields (includes Subject headings and all test fields)

retrieved. Articles that fulfilled the inclusion criteria were included in the review. Reference lists of eligible ar- ticles were searched to identify potentially relevant articles missed by the original database search. Another researcher (HJC) reviewed 10 % of the citations and ab- stracts, as well as 100 % of the full-text articles, to con- firm appropriate implementation of the eligibility criteria and accuracy of data extraction. For practical and re- source reasons a grey literature search was not per- formed, as the likelihood of finding appropriate studies not identified in retrieved citations or reviews was considered very small.

Data collection

Data were extracted from eligible studies using standardised data collection forms. Data items included study method- ology, patient information (including demographic details and definition of 'constipation' used), primary outcome data (including follow up period), duration of use of treatment, and adverse events reported. The Cochrane assessment of bias for non-randomised studies tool (ACROBAT-NRSI)
[12] was used to evaluate methodological quality and sources of bias for the included studies.

Outcomes

The primary outcome was the proportion of patients with an investigator-reported positive outcome to trans- anal irrigation therapy.

Secondary outcomes include response by constipation type, duration of treatment use and safety of treatment assessed by adverse event reporting in studies.

Analysis

Both qualitative review of study results and quantitative analysis was performed. Rates of complications are re- ported and statistical pooling of proportion estimates was explored using fixed and random effect models
within StatsDirect © Version 3. Both Q and I^2 statistics

were calculated to assess study heterogeneity. An Egger test was performed to assess risk of publication bias.

Results

Of 292 abstracts and citations reviewed, 19 full-text arti- cles were retrieved. Of these, six were suitable to be in- cluded in the review [9, 13–17]. Reference lists of these articles were reviewed and a further eligible article was identified [18], giving a total of 7 articles (Fig. 1). All eli- gible studies reported outcomes using high-volume irriga- tion only. One further study using low-volume irrigation was found, not reporting constipation-specific outcomes and was excluded from the final analysis [19]. Studies identified were prospective cohort studies, or retrospect- ive, uncontrolled case series from European nations (Table 3). In each study the patient case mix included pa- tients with faecal incontinence, soiling and following colo- rectal surgery. However the articles reported outcomes separately for each group, making it possible to evaluate outcomes for chronic functional constipation. Reported mean duration of therapy varied from 8 months

to 102 months (range 1–216 months across studies).

Studies were small, with an average number of patients per study of 36 (range 10–79); there was no evidence of a power calculation being performed for any study.

Outcome of anal irrigation therapy

Patient-reported satisfaction, either subjective or using a visual-analogue scale, was the outcome most commonly reported (5 studies) [13, 15–18]. One study used reso- lution of symptoms as the outcome measure [14], another used a combination of patient-reported symptom im- provement and ongoing use of treatment [9]. If a patient died while still using the treatment this was also consid- ered successful. One study [13] reported both patient- reported satisfaction and change in Cleveland constipation score as markers of treatment success; the patient- reported satisfaction outcome was included in this analysis as it enabled meaningful comparison with other studies.

Studies report variable response rates to therapy (Table 4). The proportion of patients who had a posi- tive outcome to therapy varied from 30 % [14] to 65 % [13, 16]. Overall, 254 patients with chronic functional constipation were included in studies, with 128 having a positive response to irrigation therapy (Table 4).

A fixed effect analysis of proportions gave a pooled re- sponse rate of 50.4 % (95 % CI: 44.3–56.5 %). Although there was no evidence of publication bias (Egger: bias = 0.259, p = 0.91), there was evidence of substantially hetero- geneity between studies ($Q[6] = 18.2$, $p = 0.0057$; $I^2 = 67.1$ %). A random effects estimate was similar, if less pre- cise: 50.9 % (95 % CI: 39.4–62.3 %), (see Fig. 2).

Four studies reported results for different sub-types of constipation (Table 5). Sample sizes in all studies were

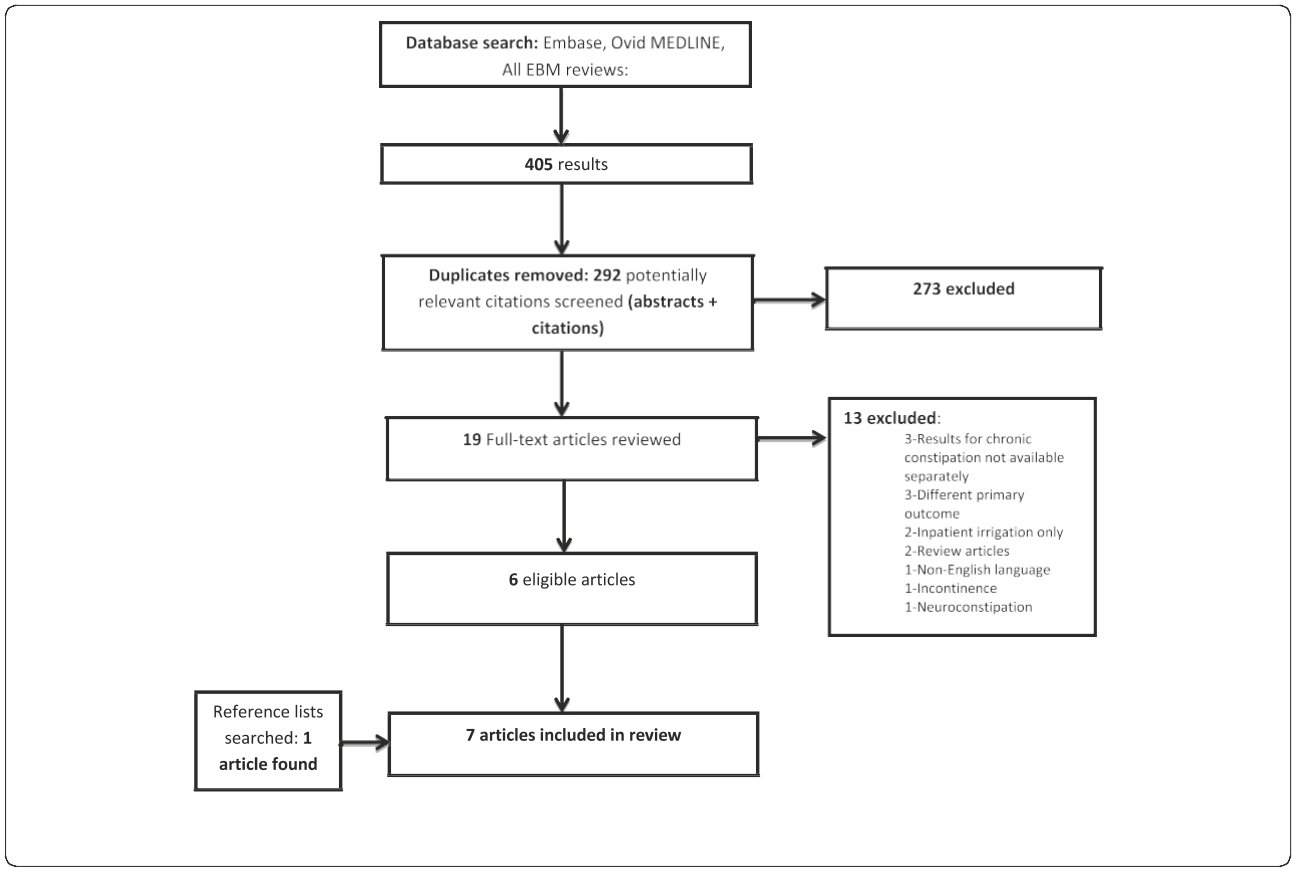
Database search: Embase, Ovid MEDLINE, All EBM reviews:
405 results
Duplicates removed: 292 potentially relevant citations screened (abstracts + citations)
273 excluded
19 Full-text articles reviewed
13 excluded:
3-Results for chronic constipation not available separately
3-Different primary outcome
2-Inpatient irrigation only
2-Review articles
1-Non-English language
1-Incontinence
1-Neuroconstipation
6 eligible articles
Reference lists searched: 1 article found
7 articles included in review

Table 3 Study characteristics

Study	Design and methods	Level of evidence[a]	Definition of constipation	Definition of successful treatment
Chan [13]	Prospective cohort study	III	Infrequent passage of stool +/− straining/ digitation/ incomplete emptying	i) → Improvement in Cleveland Constipation Score ii) → Patient-reported satisfaction
Christensen [9]	Retrospective questionnaire survey and case note review	III	Idiopathic constipation including slow transit, obstructed defecation and 'undetermined'	i) → Ongoing use ii) → Resolved symptoms iii) → Still using irrigation at time of death
Koch [14]	Prospective cohort study	III	<2 bowel motions per week, straining or incomplete evacuation >50 % motions in previous year	Resolution of incomplete emptying or straining symptoms
Cazemier [15]	Retrospective case series questionnaire survey	III	Constipation according to Rome II criteria	Patient-reported satisfaction
Gosselink [16]	Retrospective case series, questionnaire survey	III	Obstructed defecation based on; straining, incomplete evacuation, digitation, fullness, <3 motions/ week	Patient-reported satisfaction
Gardiner [18]	Case series; not stated if prospective or retrospective	III	Obstructive defecation and slow transit (?which criteria used)	Patient-reported satisfaction
Crawshaw [17]	Retrospective case note review and questionnaire survey	III	The inability to evacuate the rectum when desired (includes obstructed defecation and dyssynergic defecation)	10 mm increase on VAS (10 % improvement)

[a]Eccles, Mason 2001 How to develop costconscious guidelines [25]

Table 4 Demographics and overall response to treatment

Study	Patients with Chronic Constipation (*n*)	Average age (Years)	Male:Female	Positive response *n*(%)	Time to assessment (Months (range))	Duration of therapy (Months (range))
Chan [13]	60	46	8:52	39 (65)	6[a]	10.7[a]
Christensen [9]	79	52[a]	25:62[a]	27 (34)	21 (1–116)[a]	8 (1–85)[a]
Koch [14]	10	55.4	4:7[a]	3 (30)	3[a]	-
Cazemier [15]	12	46	1:3	6 (50)	-	102 (30–216)[a]
Gosselink [16]	37[b]	54	5:32	24 (65)	56 (8–154)[a]	[d]
Gardiner [18]	41	-	-	21 (51)	-	-
Crawshaw [17]	15	54 (41–61)[a]	13:35[a]	8 (53)	12[ac]	-
Total	254	-	-	128		

[a]Whole cohort

[b]Obstructed Defaecation only

[c]Inferred from study report

[d]Not stated, but 73 % of patients still using TAI at 30 months

-Data not available

very small (10–37 patients with OD) and and differences between sub-groups remain anecdotal. When results from all four studies where results for different types of constipation are reported are combined, there was no consistent pattern of outcome between subtypes. Methodological weaknesses, inconsistencies in out- come measures and small sample sizes limit meaning- ful comparison.

Safety of anal irrigation therapy

The most clinically significant risk associated with irriga- tion is bowel perforation. Only one study reported this complication [9] and this occurred in two patients. If re- liably reported, this represents 2 perforations in approxi- mately 110,000 irrigations, or less than 0.002 % risk per irrigation. No studies reported mortality associated with irrigation. Studies were inconsistent in their reporting of adverse events and the level of disaggregation between pathologies treated, thus only a narrative summary is possible.

Minor and self-limiting adverse events were common- place in studies but may to some extent have been toler- ated by patients, with up to 74 % of long term continuing users reporting some form of related and ex- pected adverse events in one study [16]. The most commonly- reported adverse events included abdominal cramps/discomfort (33–40 %) [9, 15, 16]; anorectal pain (5–25 %) [9, 16]; anal canal bleeding (1–20 %) [9, 13]; leakage of irrigation fluid (30–75 %) [9, 16]; and expul- sion of the rectal catheter (39 %) [9]. One study reports a 43 % incidence in 'technical problems' with irrigation [16]. In one study, 28 % of those discontinuing therapy gave side effects or technical issues with irrigation as a reason for discontinuing [9].

Therefore, whilst one or more side effects were experi- enced by a large proportion of patients undergoing anal

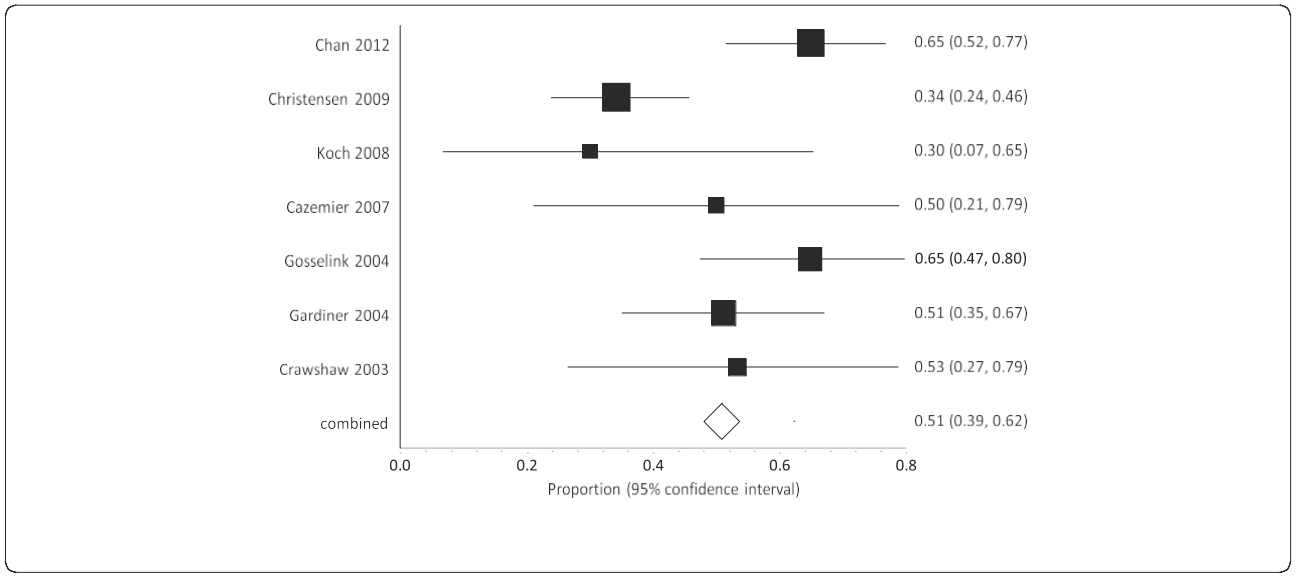
Chan 2012
Christensen 2009
Koch 2008
Cazemier 2007
Gosselink 2004
Gardiner 2004
Crawshaw 2003
combined
0.65 (0.52, 0.77)
0.34 (0.24, 0.46)
0.30 (0.07, 0.65)
0.50 (0.21, 0.79)
0.65 (0.47, 0.80)
0.51 (0.35, 0.67)
0.53 (0.27, 0.79)
0.51 (0.39, 0.62)
0.0
0.2
0.4
0.6
0.8
Proportion (95% confidence interval)

Table 5 Risk of bias assessment

Risk of bias by type

Study	Confounding	Selection	Measurement of interventions	Performance	Missing data	Measurement of outcomes	Reporting	Overall
Chan [13]	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Christensen [9]	Moderate	Moderate	Moderate	No information	Low	Serious	Low	Serious
Koch [14]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Cazemier [15]	Serious	Serious	Serious	Low	Low	Serious	Low	Serious
Gosselink [16]	Low	Serious	Moderate	Low	Moderate	Serious	Low	Serious
Gardiner [18]	No information	No information	Moderate	No information	Low	Serious	No information	Serious
Crawshaw [17]	Moderate	Serious	Serious	Low	Serious	Serious	Low	Serious

irrigation, the risk of major life-threatening, life-limiting or irreversible complications was very low.

Methodological quality

Generally, the studies were of weak methodology. There were no randomised controlled studies or case- controlled studies and most articles were retrospective questionnaire and case note based case series (Table 3). Two studies [13, 14] were prospectively designed with fixed follow up points, but numbers were relatively small (only 60 and 11 chronic functional constipation patients respectively). A further study [18] did not state whether data collection was prospective or retrospective.

Risk-of–bias assessment suggests that five studies were at serious risk of bias, and the other two were at moder- ate risk (Table 5). The retrospective questionnaire-based studies also suffered from non-response to surveys and missing data. This is likely to lead to bias and the results must be interpreted in light of this (i.e., were responders significantly more or less likely to have responded well to irrigation therapy?). Given the limitations of design and size, available studies are unable to provide robust evidence for the treatment effect of trans-anal irrigation. Patient heterogeneity was also an issue. One study in- cluded both children and adult patients together [9] and the proportion of children was not reported. Neither was it stated whether there was a difference in outcome between the adults and children. One study [15] in- cluded three patients with neurological problems in its constipation cohort, representing 25 % of this study population. As neurogenic constipation may respond dif- ferently to irrigation [20], this may have affected the re- sults. A further study included 5 patients out of 11 with chronic constipation who had had colorectal surgery (one resection and four rectopexies) [14]. Another study [17] also included patients who had undergone pelvic surgery or rectopexy in the chronic constipation cohort. It is not known precisely what effect these inclusions

had on response to treatment but these remain a poten- tial source of confounding.

Discussion

This review brings together the findings of seven pri- mary research studies which examine outcomes of trans-anal irrigation therapy in patients with chronic functional constipation.

Studies retrieved are small and not of robust methodo- logical quality; only two are prospectively-designed, and there is the potential for reporting bias in the four stud- ies that use questionnaires. This finding underlines the fact that the evidence for use of irrigation in functional constipation is currently weak.

The aggregate success rate of irrigation therapy is around 50 % based on these seven studies. Given the chronic and refractory nature of the symptoms in many of these patients this may be considered adequate, espe- cially given the simple and reversible nature of the treat- ment [8]. By comparison, response rates for drug treatments in this group of patients has been reported as 20–40 %, though these are prospective RCTs reporting symptom based primary end-points [21–23]. Addition- ally, reported response rates in neurogenic constipa- tion are only slightly higher-around 60 % [5]. Mean duration of use of treatment was reported between 8 months and 102 months. Inconsistencies in reporting findings, methodological differences and weak study design mean that there is insufficient evidence to state with any confidence exactly what the duration of bene- fit of treatment should be.

The majority of patients experience some form of ad- verse event although these are mostly minor, reversible and self-limiting. This may be a factor in determining the success of therapy: the need for high levels of patient mo- tivation, as well as support from specialist nurses, is recog- nised [8]. The rates of life threatening complications are very low throughout the studies: Irrigation can be consid- ered a safe therapy, when used with proper training.

There is insufficient evidence to state with any certainty how best to tailor therapy to patient symptoms. A recent review based on expert consensus [24] has proposed a number of regimes to overcome problems with irrigation and so improve outcomes, but experimental trial evidence is lacking, especially for functional constipation patients. In spinal cord injured patients, it has been found that emptying the rectosigmoid using irrigation stimulates co- lonic transit [24] however it is not clear whether this is transferable to patients with slow colonic transit and func- tional constipation. Scintigraphic studies have suggested that these patients have a different response to irrigation, with reduced colonic clearance compared with spinal cord injured patients [20]. In addition, none of the studies as- sess outcomes of low-volume anal irrigation systems.

Two previous systematic reviews examining trans-anal irrigation were found [8, 10]. These reviews, while valu- able, have several limitations: They focus on irrigation as a therapy for several conditions including neurogenic con- stipation, faecal incontinence, idiopathic constipation and mixed symptoms; also, one review [10] incorporates stud- ies of inpatient pulsed irrigation which is a very different therapy from home irrigation described in this review. The findings of this review are similar to the previous studies with respect to the weak nature of current evi- dence and the heterogeneity of the studies included. Sub- sequent to these reviews further studies have been identified and this review is the first to address irrigation therapy in idiopathic constipation only. This is also the first systematic review on this topic to be conducted in ac- cordance with the PRISMA statement. Additionally, this is the first meta-analysis of the effectiveness of irrigation in chronic functional constipation.

Conclusion

This review suggests that trans-anal irrigation may be an effective therapy for chronic constipation, and may be considered in patients who have not responded to medical management. Irrigation is safe and its effectiveness is at least comparable with pharmacological therapies. How- ever, the evidence to guide its use in chronic functional constipation is weak, and its long-term benefits are un- clear. There are no reported data on cost-effectiveness of irrigation: whether treatment provides good value for money from scarce health service resources. There is a clear need for well-designed prospective trials to evaluate the effectiveness, duration, and adverse consequences of treatment, as well as to assess how best to tailor therapy to individual patients. Future studies should have defined outcome measures, for example improvement in validated quality-of-life questionnaires within a defined time point. More evidence about the comparative effectiveness and cost-effectiveness of low-volume and high-volume irriga- tion systems would also be valuable.

Abbreviations

TAI: Trans-anal irrigation; ODS: Obstructed defecation syndrome;

FDD: Functional defecation disorder; CIC: Chronic idiopathic constipation; IBS-C: Irritable bowel syndrome (constipation-predominant);

PRISMA: Preferred reporting items for systematic review and meta-analysis; EBM: Evidence-based medicine; RCT: Randomised controlled trial.

Competing interests

JYY has received an educational grant from Coloplast. CDE, HJC and JMM declare no conflict of interest. The review has been accepted for poster presentation at the United European Gastroenterology Week (October 2015), and conference abstracts will be published in the United European Gastroenterology Journal. The authors declare that they have no competing interests.

Authors' contributions

CDE; study design, literature search, data collection and analysis, manuscript drafting. HJC; study design, literature search, checking accuracy of data collection, review of the manuscript. JYY: Study design, review of the manuscript. JMM; study design, statistical analysis, review of manuscript. All authors read and approved the final manuscript.

Author's information

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STUDY PROTOCOL Open Access

Low-volume versus high-volume initiated trans-anal irrigation therapy in adults with chronic constipation: study protocol for a randomised controlled trial

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Abstract

Background: Constipation is common in adults and up to 20% of the population report this symptom. Chronic constipation (CC), usually defined as more than 6 months of symptoms, is less common but results in 0.5 million UK GP consultations per annum. The effect of symptoms on measured quality of life (QOL) is significant, and CC consumes significant health care resources. In the UK, it is estimated that 10% of district nursing time is spent on constipation. Trans-anal irrigation therapy has become a widely used treatment despite a lack of robust efficacy data to support its use. The long-term outcome of treatment is also unclear. A randomised comparison of two different methods of irrigation (high- and low-volume) will provide valuable evidence of superiority of one system over the other, as well as providing efficacy data for the treatment as a whole.

Methods: Participants will be recruited based on predetermined eligibility criteria. Following informed consent, they will be randomised to either high-volume (HV) or low-volume (LV) irrigation and undergo standardised radiological and physiological investigations. Following training, they will commence home irrigation with the allocated device. Data will be collected at 1, 3, 6 and 12 months according to a standardised outcomes framework. The primary outcome is PAC-QOL, measured at 3 months. The study is powered to detect a 10% difference in outcome between systems at 3 months; this means that 300 patients will need to be recruited.

Discussion: This study will be the first randomised comparison of two different methods of trans-anal irrigation. It will also be the largest prospective study of CC patients treated with irrigation. It will provide evidence for the effectiveness of irrigation in the treatment of CC, as well as the comparative effectiveness of the two methods. This will enable more cost-effective and evidence-based use of irrigation. Also, the results will be combined with the other studies in the CapaCiTY programme to generate an evidence-based treatment algorithm for CC in adults.

Trial registration: ISRCTN, identifier: ISRCTN11093872. Registered on 11 November 2015. Trial not retrospectively registered. Protocol version 3 (22 January 2016).

Keywords: Constipation, Irrigation, Chronic

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Background

Burden of disease

Constipation is common in adults and up to 20% of the population report this symptom depending on the defi- nitions used [1–3], with a higher prevalence in women [1, 4, 5] and older people [6, 7]. Chronic constipation (CC), usually defined as more than 6 months of symp- toms, is less common [8] but results in 0.5 million UK GP consultations per annum. A proportion of the popu- lation suffer symptoms which are both chronic and more disabling (about 1–2% of the population) [9]. Such pa- tients, who are predominantly female [10], are usually referred to secondary care with many progressing to ter- tiary specialist investigation. Patient dissatisfaction is high in this group; nearly 80% feel that laxative therapy is unsatisfactory [11] and the effect of symptoms on measured quality of life (QOL) is significant [12]. CC consumes significant health care resources. In the US in 2012, a primary complaint of constipation was respon- sible for 3.2 million physician visits [13] resulting in (direct and indirect) costs of US$1.7 billion. In the UK, it is estimated that 10% of district nursing time is spent on constipation [14] and the annual spend on laxatives exceeds £80 million, with 17.4 million prescriptions be- ing issued in 2012 (Health and Social Care Information Centre, 2013) [15].

Pathophysiological basis of chronic constipation

The act of defaecation is dependent on the coordi- nated functions of the colon, rectum and anus. Con- sidering the complexity of neuromuscular (sensory and motor) functions required to achieve planned, conscious and effective defaecation [16] it is no sur- prise that disturbances to perceived ‘normal’ function occur commonly at all stages of life. Clinically, such problems commonly lead to symptoms of obstructed defaecation, e.g. straining; incomplete, unsuccessful or painful evacuation; bowel infrequency; abdominal pain and bloating. After exclusion of a multitude of sec- ondary causes (obstructing colonic lesions, neurological, metabolic and endocrine disorders), the pathophysiology of CC can broadly be divided into problems of co- lonic contractile activity and thus stool transit and problems of the pelvic floor. Thus, with specialist physiological testing (using a standard panel of radio- physiological tests of colonic and anorectal function, hereafter referred to as INVEST in this protocol), pa- tients may be divided into those who have slow co- lonic transit, evacuation disorder, both or neither (no abnormality found with current tests). Evacuation dis- orders can be then subdivided into those in which a structurally significant pelvic floor abnormality is evident,
e.g. rectocoele or internal prolapse (intussusception) and those in which there is a dynamic failure of evacuation

without structural abnormality: most commonly termed
'functional defaecation disorder (FDD)'.

Chronic constipation management overview

Management of CC is a major problem due to its high prevalence and lack of widespread specialist expertise. In general, a step-wise approach is undertaken, with first- line conservative treatment, such as lifestyle advice and laxatives (primary care), followed by nurse-led bowel retraining programmes, sometimes including focussed biofeedback and psychosocial support (secondary/tertiary care). Although these treatments may improve symptoms in more than half of patients, they are very poorly standar- dised in the UK and are not universally successful [17]. Thus, patients with intractable symptoms and impaired QOL may be offered a range of costly, irreversible surgical interventions with unpredictable results [18, 19], some- times resulting in major adverse events (AEs) or a per- manent stoma.

Overall rationale for the CapaCiTY programme

The current trial forms part of an NIHR-funded programme (PGfAR: RP-PG-0612-20001). This prog- ramme aims to develop the evidence base for the man- agement of CC in adults which is currently lacking. This is in contrast to the management of CC in children for which NICE guidance has been recently published (http://pathways.nice.org.uk/pathways/constipation/clinical- management-of-idiopathic-constipation-in-children-and- young-people) [20, 21]; and for adults with faecal incontinence (http://pathways.nice.org.uk/pathways/faecal-incontin- ence). Thus, the current situation is one where there are considerable variations in practice, particularly in specialist services. With a number of new drugs gaining or seeking NHS approval [22–25] and technologies at a horizon- scanning stage [18, 26, 27] it is timely that the currently limited evidence base for adult CC is developed for resource-constrained NHS providers to have confidence that new and sometimes expensive investigations and ther- apies are appropriate and cost-effective. A cost-conscious pathway of care may help to reduce health care expenditure by appropriately sequencing the care provided, while target- ing more expensive therapies at those most likely to benefit. Such data will inform the development and commissioning of integrated care pathways. An overview of the CapaCiTY programme is provided as a scheme (See Additional file 1) and includes a series of interlinked work package signature pages (WPs) that answer the important questions for pa- tient care. A rolling programme of national recruitment will provide a large cohort of well-defined patients for subse- quent studies within sequential WPs over 5 years. The focus will be on generating real-life evidence from prag- matic studies which will provide valid clinical outcome measures, patient acceptability and cost. Armed with such data it will be possible to develop an NHS management algorithm for CC which will meet patient, clinician and policy aims.

Specific clinical background to the prospective cohort study of trans-anal irrigation (TAI)

Anal irrigation, using a variety of commercially available devices, has been rapidly disseminated internationally over the past 3–5 years, first in patients with neuro- logical injury [28, 29] and subsequently in other CC groups [30, 31]. Despite a lack of published data other than from small selected case series, it is now available on the drug tariff and generally considered to be the next step in patients failing other nurse-led interventions such as biofeedback. Anal irrigation has permeated the UK market without robust efficacy data and with on- going concerns regarding longevity of treatment and complications [28, 32]. Retrospective clinical audit data and review [32] suggest a

continued response rate after 1 year of approximately 50% with such patients, thus avoiding or delaying surgical intervention. An accurate assessment of response rate and acceptability of this intervention requires confirmation in a large prospective cohort, together with clinico-physiological predictors of success. In addition, two alternative systems for delivery of TAI exist; low-volume systems delivering approxi- mately 70 ml per irrigation, and high-volume systems delivering up to 2 L of irrigation (although typically only 0.5–1.5 L is required per irrigation). The low-volume system is cheaper, costing approximately £750 p.a. based on alternate-day use, compared with approximately £1400–1900 for high-volume irrigation, and may be more acceptable to patients, and so a randomised study comparing the two systems is needed.

Trial design: rationale

Robust data for the use of TAI therapy in chronic (idiopathic) constipation are lacking. In addition, there are no data demonstrating superiority of high-volume ir- rigation over low-volume systems. Given the differences in cost between the two systems, a randomised study of well-characterised patients comparing the two methods would provide useful information on whether one sys- tem holds a clear advantage over the other. Also, the short- and long-term efficacy and acceptability of ther- apy in CC could be evaluated. This is timely and inform- ative given the rapidly increasing popularity of this treatment and the fact that TAI is an invasive therapy for which patient selection should also be optimised to maximise benefit.

In practice, patients will use one system only (plus de- fined 'rescue therapies' – see below) for a minimum of 3 months. After this time point they may switch to the other system if their initial therapy was ineffective/ unsatisfactory. Thus, consenting patients will be rando- mised to initiate therapy with one of these systems but will have the option of switching to the other after an initial 3-month period. This allows us to identify re- sponse rates to each system in the short term (3 months), and thereafter this study is a comparison between treat- ment strategies (low-volume initiated therapy versus high-volume initiated therapy) rather than a pure com- parison of the two techniques. This is a patient-centred study design aiming to limit the time that patients spend using ineffective therapy without being allowed to try an alternative. This also allows estimation of comparative cost-effectiveness of the two treatment pathways, and whether one system works better depending on the radio-physiological profile of the patient. Recent data es- timates that approximately 85% of patients are still using irrigation at 1 month; this represents a significant short- term treatment failure rate [33]. Once patients have switched therapy, they may not switch back to the first system; once they have tried both systems and discontin- ued them then they will be considered to have com- pleted the intervention and they will return to routine clinical care.

Irrigation is a maintenance therapy rather than a cure. In addition to outcome measures of the Patient Assessment of Constipation Quality of Life question- naire (PAC-QOL) [34, 35] score at 3 months, patients will provide survival data (time until cessation of irriga- tion therapy due to lack of benefit). Switching systems does not affect this; the survival data is based on the use of irrigation irrespective of system. A survival analysis is appropriate since anal irrigation is time-consuming and inconvenient as a therapy and patients may find the process distasteful. Patients are unlikely to continue with treatment if they are not gaining worthwhile benefit from it; treatment continuation is a useful patient- centric assessment.

Consideration of the findings from both groups (individually and together) will be

used to model the net value to patients of anal irrigation, considering persist- ence of benefit.

Risks/benefits

The interventions proposed are those already offered to patients in specialist centres throughout the UK and internationally. All interventions pose acceptable and minimal risks. For instance, functioning; however, all have been used in studies of similar patients previously.

Trans-anal irrigation has been shown to be a low- risk intervention and is widely used in a variety of defaecatory disorders such as neurogenic bowel dys- function, idiopathic constipation and faecal incontin- ence. Serious adverse events (SAEs) are rare, with one study reporting two nonfatal bowel perforations out of approximately 110,000 irrigation treatments [28]. Other potential side effects include pain, bleeding, painful haemorrhoids and anal fissure. A recent study reported an overall adverse event (AE) rate of 22% when all minor and reversible events were considered. Thirteen percent reported technical problems with equipment and 13% reported minor side effects/AEs [33]. The risk of nonparticipation is considered very low.

The benefits of participation are that patients will re- ceive a very high standard of monitored care as a conse- quence of the detailed protocol. Participation will inform future treatment options for patients with CC.

Trial objectives

Primary objectives

1. To compare the impact upon patient disease-specific QOL of TAI initiated with a low-volume versus a high-volume system in patients with CC, measured at 3 months

the only invasive tests (INVEST) have been performed daily in most specialist centres for up to 30 years without any recorded compli- cation (Barts Health experience of over 10,000 patients). A small ionising radiation dose is required for one of the tests (covered below). A number of questionnaires contain personal questions about bowel problems and the effect of these on QOL and psycho-behavioural

Secondary objectives

To determine:

1. Survival (continuation of benefit) and acceptability in the longer term (up to 12 months)
2. Disease-specific outcomes at 1, 3, 6 and 12 months
3. The influence of patient characteristics (urge to defaecate, balloon sensory testing results) upon treatment success, and response by type of system used
4. The acceptability of each system to patients
5. Strategies for tailoring therapy to meet patients' individual needs, and the factors involved in this
6. The safety of each system and prospective tracking of AEs
7. The cost-effectiveness of care
8. Qualitatively evaluation of patient and health professional experience

Methods

Setting

Specialist centres across the UK with a mix of urban and rural referral bases

Recruiting sites (initial)

- Barts Health NHS Trust [Allison]
- St. Mark's Hospital at London North West Healthcare NHS Trust [Vaizey]
- University College Hospital London [Emmanuel]
- Guys and Thomas' Hospitals London [Williams]
- Sandwell and West Birmingham NHS Trust [Gill]
- County Durham and Darlington NHS Foundation Trust [Yiannakou]
- University Hospital Southampton NHS Foundation Trust [Nugent]
- Norfolk and Norwich University Hospitals NHS Foundation Trust [Speakman]
- University Hospital of South Manchester NHS Foundation Trust [Telford]
- Sheffield Teaching Hospital NHS Foundation Trust [Brown]
- North Bristol NHS Foundation Trust [Dixon]
- University Hospitals Bristol, NHS Foundation Trust [Mabey/Randall]
- Newcastle Upon Tyne, NHS Foundation Trust [Plusa]
- Homerton University Hospital, NHS Foundation Trust [Cuming]

Reserve sites

- University Hospital Leicester NHS Foundation Trust

[Miller]

Central facilities

- Bart's and the London, Pragmatic Clinical Trials Unit. Centre for Primary Care and Public Health, Queen Mary University London (QMUL)
- County Durham and Darlington NHS Foundation Trust, Durham Clinical Trials Unit. Wolfson Research Institute, Durham University

Inclusion criteria

- Age 18–70 years
- Patient self-reports problematic constipation
- Symptom onset more than 6 months before recruitment
- Symptoms meet American College of Gastroenterology definition of constipation
- Nonresponse to constipation treatment to a minimum basic standard (see NHS Map of Medicine 2012) [36]: Comprising lifestyle *and* dietary measures *and* two or more laxatives or prokinetics tried (no time requirement)
- Ability to understand written and spoken English (due to questionnaire validity)
- Ability and willingness to give informed consent
- Failure of previous nurse-led behavioural therapy
- Ability of patient/carer to use anal irrigation

The study will use the American College of Gastro- enterology definition of constipation [37] (which is reasonable, simple and extensively published): unsatisfac- tory defaecation characterised by infrequent stool, difficult stool passage or both for at least previous 3 months. This avoids the more complex Rome definitions.

Exclusion criteria

The study interventions necessitate the exclusion of major causes of secondary constipation. In detail:

- Significant organic colonic disease ('red flag' symptoms, e.g. rectal bleeding previously investigated); inflammatory bowel disease (IBD); megacolon or megarectum (if diagnosed beforehand) (the study will provide a useful estimate of the prevalence of such cases in referral practice); severe diverticulosis/ stricture/birth defects deemed to contribute to symptoms (incidental diverticulosis not an exclusion)
- Major colorectal resectional surgery
- Current overt pelvic organ prolapse (bladder, uterus, vagina, rectum) or disease requiring surgical intervention
- Previous pelvic floor surgery to address defaecatory problems: posterior vaginal repair, STARR and rectopexy; previous sacral nerve stimulation
- Previous use of TAI therapy to treat constipation
- Rectal impaction (as defined by digital and abdominal examination: these form part of the NHS Map of Medicine basic standard) [36]
- Significant neurological disease deemed to be causative of constipation, e.g. Parkinson's disease, spinal injury, multiple sclerosis, diabetic neuropathy (not uncomplicated diabetes alone)
- Significant connective tissue disease: scleroderma, systemic sclerosis and SLE (not hypermobility alone)

- Significant medical comorbidities and activity of daily living impairment (based on Bartell index in apparently frail patients [38], Barthel Index ≤11)
- Physical disability/impairment which prevents the use of one or other of the irrigation devices
- Major psychiatric diagnosis (schizophrenia, major depressive illness, mania, self-harm, drug/alcohol addiction)
- Chronic regular opioid use (at least once daily use) where this is deemed to be the cause of constipation based on temporal association of symptoms with onset of therapy; all regular strong opioid use
- Pregnancy or intention to become pregnant during study period

Note: 'red flag' symptoms are not an exclusion if they have been investigated before enrollment and organic disease excluded. Previous TAI therapy does not include private (non-NHS) 'colonic irrigation' therapy; prior use of such treatments is not an exclusion criterion.

Study interventions: trans-anal irrigation therapy

Trans-anal irrigation training will be provided by trained nurse or physiotherapist with experience in delivering care for CC. They must have initiated irrigation therapy in at least three patients independently, and be a nurse/therapist of good standing within a clinical team regularly seeing pa- tients with CC. A standardised approach and intervention will be provided via the use of an intervention manual. For the first 3 months of participation in the study, patients may not use other therapies besides anal irrigation and those rescue therapies specified below. They may discon- tinue therapy at any point (elective withdrawal from inter- vention) and may switch from one system to the other after 3 months. Switching anal irrigation systems before completing the 3-month waiting period will be discour- aged. If it does occur, it will be documented as a protocol deviation with the timing and reason documented. If symptoms are severe despite the use of irrigation and res- cue therapies then other medications may be used on com- passionate grounds, but this must be recorded in the Case Report Form(CRF)/concomitant medications log.

The course of therapy will include a nurse-led training session (or more if required to ensure that the device is being used effectively) followed by patient-led home irri- gation therapy. The low-volume system commonly used in practice is Qufora® Mini (MBH-International). Various high-volume systems are used, all of which have very similar mechanisms of action; these include Peristeen™ (Coloplast) and Qufora Toilet/Qufora Balloon™ (MBH- international). These are commercially available TAI sys- tems available on prescription in NHS practice.

Low-volume irrigation

This system consists of a small reservoir attached to a cone. The reservoir holds approximately 70 ml of water and is squeezed to inject water into the rectum. The re- gime used will be as follows: initial irrigation once daily for 14 days using one to three insufflations (each of 70 ml approximately). This may then be reduced to alternate days depending on response. Patients may then adjust fre- quency and volume depending on response. They may irrigate as much and as often as they feel is necessary to give them benefit and this information will be captured on the CRF with the aid of an Irrigation Journal.

High-volume irrigation

High-volume systems consist of an irrigation bag con- nected to a tube. The water flows into the rectum,

either by gravity or using a pump. Some systems em- ploy a balloon to hold the device in place during irri- gation; others require the patient to hold it in place. The mechanism of action is the same for all systems. Initial frequency of irrigation is the same as for low- volume irrigation; i.e. daily for 14 days, then alternate days. Patients will commence with irrigations of 300 ml and increase this by 100 ml every 2 days until satisfactory defaecation is achieved or the procedure becomes uncomfortable, up to a maximum of 1500 ml. Patients may adjust therapy depending on response, as for low-volume irrigation.

Switching between anal irrigation systems

After 3 months of using one system, patients may switch to the other or discontinue therapy and return to routine clinical care. This will be entirely patient-led, and reasons for changing systems will be ex- plored during follow-up visits and captured on the CRF. There is, therefore, no defined protocol for switching treatments as patients may do this for any reason; analysis of time to switching/discontinuing therapy, as well as the patient-reported reasons for doing so, will provide insight into why each irrigation system is or is not successful. In addition, qualitative interviews with patients who have switched or discontinued therapy will be used to explore these issues more deeply.

Endpoints

Clinical endpoints

All clinical endpoints will be in common with a single standardised outcome framework (consistently used within all CapaCiTY programme studies). All outcomes will be recorded at baseline, 3, 6 and 12 months in face- to-face clinics (or by telephone call if necessary). PAC- QOL, the Patient Assessment of Constipation Symptoms (PAC-SYM) and the EuroQol Health Outcome measure (EQ-5D-5 L) and the EuroQol Visual Analogue Scale (EQ-VAS) will additionally be collected at 1 month; this is to capture reasons for early nonresponse to therapy, as well as to better characterise the patient group and provide more data for economic analysis. The primary endpoint will be at 3 months.

Primary clinical outcome

- Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL [34, 35]) at 3 months.

Secondary clinical outcomes

- PAC-QOL score and individual domain scores at 1, 3, 6 and 12 months

- Time to cessation of each system of irrigation; total time in treatment with either system (from Irrigation Journal) at 1, 3, 6 or 12 months
- Reason for cessation (of each system) (Irrigation Journal and qualitative interviews) at 1, 3, 6 and 12 months
- Patient Assessment of Constipation Symptoms (PAC-SYM): aggregate and domain scores at 1, 3, 6 and 12 months
- Volume and duration of irrigation (Irrigation Journal) at 1, 3, 6 and 12 months
- Number and nature of bowel motions (captured in 2-week Patient Diary) at 3, 6 and 12 months
- Symptom scores derived from Diary records (taken over 2 weeks before or around each follow-up contact. These will include number of spontaneous complete bowel motions at 3, 6 and 12 months
- Generalised Anxiety Disorder Questionnaire (GAD-7) at 3, 6 and 12 months
- Depression, anxiety and somatisation modules of the PHQ-9 at 3, 6 and 12 months
- Global patient satisfaction/improvement score (Visual Analogue Scale; VAS) at 3, 6 and 12 months
- Patient acceptability and recommendation to other patients (qualitative interviews)
- Behavioural Response to Illness Questionnaire (CC- BRQ) and Brief Illness Perception Questionnaire BIPQ (CC) at 3, 6 and 12 months

saturation when no new themes emerge.
Participants will be approached by a member of the research team and will undergo a separate consent process if they are willing to participate in the qualitative study.

Study design/plan – Study visits

The following section provides an overview of patient study visits. This is provided in diagrammatic format in the attached Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure (Fig. 1. See Additional file 2 for the SPIRIT Checklist).

Visit 0: Prescreening: eligibility assessment

- Generic quality of life: EuroQol EQ-5D-5 L and EQ-VAS scores 1, 3, 6, and 12 months
- Use of health care resources, AEs, and concomitant medications (collected using Patient Journal) at 3, 6 and 12 months

Health economic outcomes

- Interventions, treatment sequelae and other health resource use related to the care of CC will be recorded in natural units and cost applied where possible using national reference costs. Additionally, patient costs related to constipation and the opportunity cost of time away from normal activities will be valued using national reference sources.

Patient experience (see 'Qualitative interviews')

- Face-to-face, digitally recorded, semistructured interviews will be conducted involving a purposive, diverse sample of patients throughout the programme, with participants reflecting a range of ages, geographical locations and, where possible, other pertinent attributes, such as ethnicity and gender, continuing until data

A Good Clinical Practice (GCP)-trained and dele- gated local researcher will screen for basic eligibility by telephone (or face-to-face interview based on pa- tient choice). Potentially eligible patients will be identified either in clinic, from referral letters from GPs/other consultants to the constipation clinic, and from patients participating in CapaCiTY 01 who did not respond, or have ceased to respond, to habit training (HT)/biofeedback (HTBF). Participants will be provided with adequate explanation of the aims, methods, anticipated benefits and risks of anal irriga- tion therapy and will take away or be posted an invi- tation letter and a Participant Information Sheet (PIS). Patients will be given at least 24 h to consider participation and invited to attend clinic for visit 1 (see below).

The study screening number will be allocated as follows:

- Study code 02
- Site code – three-letter code for each site
- Participant Code – four-digit code given consecutively and attributed at each site

For example, the first participant recruited at Barts Health Trust would be assigned the code 02-BLT-0001. Patients progressing to other studies within the CapaCiTY programme will keep this number for pathway tracking.

Visit 1: Screening, consent, baseline assessments and randomisation

Visit 1 will be conducted face to face in clinic. Following a detailed discussion about the trial, potentially eligible and agreeable patients will complete a written informed consent, followed by a more thorough screening and confirmation of eligibility for randomisation by standar- dised medical and surgical history and physical examination (the latter if not already performed within the previous 3 months).

Patients who decide not to opt for treatment will be invited to offer reasons and these will be recorded when provided. Patients declining participation will continue to receive usual care as locally provided. There is no obligation for patients to give reasons for nonparticipation.

Assessment	V0	V1 Screening &	V2	V2.1 (V2.2**)	V3 1 month	V4	V5	V6
Brief screening and providing PIS Informed Consent	x	x						
Structured history including eligibility assessment, demographics, medical history, medications, clinical examinations		x						
Pregnancy Test where applicable Baseline only assessments Rectal balloon sensory testing* Balloon expulsion test* Anal manometry*		x x	x	x	x	x	x	x
Radio-opaque marker transit study*		x	x		x	x	x	x
Randomisation		x				x	x	x
In therapy assessments (Anal Irrigation)**			x		x	x	x	
						x	x	
Adverse Event and Concomitant Medication Review		x	x	x				

`V1.1 = INVEST – A minimum timeframe of 2 weeks to allow completion of baseline diary prior to INVEST and maximum of 8 weeks (for logistical purposes).
V2 = commencement of therapy and TAI training; V2.1 = Phone call within 2 weeks

**V2.2 = further training if needed to be conducted prior to or in conjunction with V3 if necessary. V3 = 4 week follow up session (Face-to-face if possible or telephone)
All follow up time points measured from commencement of therapy (V2)

For those patients entering the study, additional base- line outcome assessments will be conducted. These in- clude several key validated assessments that profile patient characteristics, informing disease pathophysi- ology and potential predictors of treatment response. All have been selected on the basis of trade-off between ad- equate detail and achievable brevity. These instruments will be combined with the standardised outcome frame- work into a single booklet (design and presentation have been optimised by patient representatives).

Confirmation of eligibility

- Standardised history by interview including previous medication usage
- Clinical examination findings (carried forward if

performed previously within last 3 months): standardised exam of perineum/anus/rectum

Baseline outcome assessments

- Baseline outcome assessments (PAC-QOL, PAC-SYM, EQ-5D-5 L and EQ-VAS, PHQ-9, GAD-7, CC-BRQ and BIPQ-CC, see endpoints above)
- Baseline 2-week Patient Diary will be given. Training in completion of the diary will be conducted at visit 1 and the diary will be completed at home and returned at visit 2
- Training and retrospective completion of the Patient Journal will occur at visit 1 for collection of resource data. Prospective completion will occur continuously, with review at each follow-up visit from 3 to 12 months

Other baseline only assessments

- Constipation (2006) and IBS (2006) modules of the Rome III Questionnaire
- Cleveland Clinic Constipation Questionnaire
- Brief, chronic pain, autonomic and joint hypermobility assessments
- St. Mark's Incontinence Score (for concurrent symptoms)

Randomisation

Conducted by a member of the research team.

INVEST radio-physiology investigations

There is no defined time period for this, but it is sug- gested that INVEST should be completed within 4 weeks of the visit 1 baseline visit to allow for diary completion before stopping laxatives for INVEST. A maximum of 8 weeks is tolerated to conduct INVEST. Those with INVEST completed in the previous 12 months do not need these repeated and can be booked for visit 2, com- mencing in a minimum of 2 weeks to allow completion of the baseline diary.

Training sessions (45–60 min) (V2–V3)

This will use a standardised proforma and will always be face to face. Patients will receive:

Visit 2: First training session

Visit 2.0

1. Collection of baseline diary completed before stopping laxative (i.e. before INVEST in patients who need this done)
2. Training in TAI: patients will undergo a single, nurse-led training session before starting treatment.
   The device will be demonstrated to the patient by the nurse specialist and then the patient will practice setting up the device. The trainer will ensure that the patient knows how to use the device correctly before home irrigation is commenced
3. Training in completion of the Irrigation Journal and provision of the Irrigation Journal to be completed weekly. The Irrigation Journal consists of: volume of water introduced, frequency of use, AEs and side effects, e.g. pain, bleeding
4. The trainer and patient will agree a date for delivery of equipment and commencement of home irrigation. Ideally, this should be the same as the first training visit, but this may not be possible due to delay in supplying irrigation equipment. Any delays should be recorded on a deviation log/note to file (CRF 7/8) to allow data analysis to be adjusted accordingly
5. Start date for home irrigation agreed with the patient (this is to allow for any delay in delivery of equipment). Ideally this should be the same day as visit 2, or within 1 week maximum. If any issues or delays have been encountered, a new commencement date is agreed; this should be recorded as a deviation/ note to file (CRF 7/8), along with reasons for delay
6. Regulation/standardisation of laxative use: bisacodyl may be used orally as a rescue therapy (up to 20 mg at night), plus glycerine suppositories, one or two, if needed, if no stool for 3 days. In addition, patients may take Movicol up to a

maximum dose of two sachets three times per day (TDS) and/or lactulose up to 15 ml twice per day (BD). Prokinetic drugs and any other drug that the *British National Formulary* (BNF) describes as having laxative effect or herbal teas that contain strong purgatives will be discouraged, but if needed (i.e. if symptoms severe) then these are permitted but use must be recorded in the concomitant medications log. There will be no use of enemas.

Visit 2.1: First intervention assessment

A telephone call will be made to the patient 14 days (±3 days) after visit 2 to check that everything is pro- ceeding correctly and to resolve any problems. If, due to delay in obtaining equipment, etc., the patient has not started irrigation at this time then the telephone call (and other follow-up visits) should be rescheduled for 14 days later, and the reason for this recorded on CRF 7/8. Adverse events and concomitant medications will also be reviewed.

Visit 2.2: Second intervention assessment (if needed)

If there are problems then a further face-to-face training session will be offered, including a review of AEs and concomitant medications. This can occur any time be- fore visit 3 (2 weeks ±1 week from visit 2.1) or in con- junction with visit 3 if not before.

Patients will continue the self-administered therapy using a commercially available device until the end of the study. Patients will be followed up until the end of the data collection phase of the study (variable follow-up 12–24 months depending on date of recruitment) or until they decide to discontinue either the therapy or the trial follow-up. Irrigation will be performed at an agreed frequency initially. Once established on this therapy pa- tients may adjust the frequency and volume of irrigation to suit their particular condition.

Information about treatment will be recorded in the Irrigation Journal. Where a patient switches to the other irrigation device or discontinues treatment (patient choice) the reason for this, as well as the duration of therapy, will be documented. If a patient chooses to switch devices, which they may do at any stage after the 3-month follow-up visit, they will receive training in the other device. They will receive a follow-up by the irriga- tion nurse as required to resolve any outstanding issues and to check progress. This should be documented on the Irrigation Journal and a note to file, (CRF 8) and change/discontinue, (CRF 12) should be completed. However, they will not be asked to repeat the question- naires and diaries already completed at 1 and 3 months.

Visit 3: 1-month follow-up review

1. All patients will receive a further training assessment at 2 weeks (±1 week) after visit 2.1, allowing for any delay as described previously (V3). This visit will be combined with collection of PAC-QOL, PAC-SYM and EQ-5D-5 L and EQ-VAS and should be face to face. The Irrigation Journal will be reviewed at this visit. A telephone call is an acceptable alternative if this is not possible
2. Standardised guidance on how to tailor therapy to each patient depending on initial response will be

provided to specialist nurses/therapists. Changes in regimen, as well as system, will be documented on the CRF. As outlined previously, switching between irrigation systems before the 3-month visit is discouraged, and represents a protocol deviation.
However, it is recognised that some patients may need to switch systems before 3 months: if this occurs it must be recorded on CRF 12 and on the deviation log. Primary outcome analysis at 3 months will be by intention-to-treat

Telephone support will be available from the therapist between visits (number given, office hours only). The therapist will complete the intervention CRF at every visit or patient contact. For contact with patients after the training period, a note to file (CRF 8) should be completed, and the patient will also make a note of any contact in their Irrigation Journal. In the instance of new psychological issues being determined during consult- ation, referral for psychological support will be deferred until after completion of irrigation training. The excep- tion to this rule would be where there is clinical concern regarding the patient's acute mental state requiring more urgent intervention (see 'Criteria for withdrawal from treatment'). Concerns would be raised by the irrigation nurse team to the research team, and these would be evaluated by the principal investigator (PI) (or a medic- ally trained deputy) and appropriate action taken. Fur- ther follow-up visits (V4–V8) will be conducted by the research team. If the patient requires further input from the irrigation nurse this may be arranged as per local practices. Any contact and any changes made or advice given regarding irrigation should be recorded in the Patient Journal and the Irrigation Journal.

Visits 4–6: Follow-up outcome assessments: visits or telephone consultations

A full, standardised outcome framework and health eco- nomic dataset will be recorded at baseline, 3, 6 and 12 months (±1 week) after initiation of intervention at visit 2. To maximise completeness of data collected, follow-up visits will be conducted face-to-face in clinic wherever possible. Where this is not possible, a tele- phone consultation will be used. The Patient Diary and Journal and Irrigation Journal will be provided for review at each follow-up visit.

Patients deciding to switch to the alternative system will be trained in the new system by the irrigation nurse and this will be recorded on the note to file, CRF 8 and change/discontinue, CRF 12. These patients will not need to complete the questionnaires at 1 month and 3 months if they have already done so.

Within the follow-up period at least three attempts via two different methods (e.g. telephone and letter), will be

made by research staff to make contact and collect follow-up data at each time point, after which the time point will be recorded as missing.

Recruitment and strategies for achieving enrollment

Patients attending specialist centres (outpatient clinics, gastrointestinal (GI) physiology units) for constipation and who have already failed to respond to a minimum basic standard of treatment (see above), as well as nurse- led interventions (biofeedback or habit training), will be eligible for recruitment screening based on criteria. Patients will be recruited from those failing treatment in CapaCiTY 01 but also those patients seen outside the trial who have had nurse-led behavioural therapies without response.

Trial posters will be displayed in primary care, phar- macy and community care settings, directing patients to their nearest research site and contact person, as well as the study website for more information, including the PIS. The same posters may be used to advertise the study via newspapers, trial websites, social media, and patient groups such as Bowel and Cancer Research charity.

Patient and Public Involvement (PPI) consultation with CC patients in secondary care has explored the ac- ceptability of this study design, and we have found that this is likely to be acceptable to patients. The proposed rescue therapy and patient diaries/journals used in the study have been reviewed as part of this process. Care has been taken to ensure that the study design is patient-centred, with flexibility of laxative use incorpo- rated into the protocol, as well as the option to switch treatment after 3 months. This aims to ensure that pa- tient experience of the trial is similar to a nontrial patient in terms of treatment received, within the con- straints of a randomised trial.

Study procedures

Screening, enrollment

A brief screening questionnaire will be used to determine whether patients meet the inclusion and exclusion criteria (see 'Eligibility' above). Screening will be performed by suitably trained study personnel to minimise logistic hur- dles, and as determined by geographic availability.

The brief screening questionnaire will also be made available on the study website, with the PIS for patients to self-screen and contact their nearest research site if inter- ested in taking part. All basically eligible participants will then undergo a formal face-to-face consent, screening and enrollment session prior to randomisation.

Randomisation procedures

Patients will be randomised 1:1 into two groups; those who commence therapy with a low-volume device and

those starting with a high-volume device. Patients will be stratified by sex and women by centre. Randomisa- tion will be performed by a GCP-trained member of the research team using a bespoke, secure online system de- veloped by the Pragmatic Clinical Trials Unit (PCTU).

Blinding

Patients and clinicians are necessarily aware of both INVEST and treatment allocations. The need to collect data on frequency and volume of irrigation, as well as reasons for discontinuing or switching between systems, means that assessor blinding is not possible with respect to these outcomes. Those involved in the development of the statistical analysis plan (SAP) will not have access to any data that will lead them to become unblended and, therefore, they will remain blind. Any researcher collecting CRFs, handling journals or performing statis- tical analysis on the above outcomes will be unblinded. However, in order to control for observer bias, the pri- mary outcome (PAC-QOL at 3 months) will be con- cealed; the patients will complete this questionnaire without a researcher present. This will be accomplished in one of the following ways:

1. Direct entry to online secure database, with built-in validation and prompting to ensure data completeness
2. Completing paper questionnaire by following instructions on an information card to ensure that all questions are answered. This will be placed in a sealed envelope marked with the patients pseudonymised study code and will not be opened until the time comes for data entry

Radio-physiological investigations (INVEST)

Patients will undergo standardised investigations. If INVEST previously conducted within the last 12 months, results can be carried forward. Pregnancy testing will be conducted as per routine NHS practice (10-day NHS rule) in respect to women between menarche and meno- pause. Women of equivocal status will have a pregnancy test performed as per routine care.

1. Anorectal manometry using standard or high-resolution methods [39–41], depending on local availability, to determine defined abnormalities of recto-anal pressure gradient during simulated evacuation [42–44]
2. Balloon sensory testing using standardised methods [45, 46] (2 ml air per second to maximum 360 ml) to determine volume inflated to first constant sensation, defaecatory desire and maximum tolerated volumes. Rectal hyposensation and hypersensation, defined in accord to gender-specific normative data on 91 healthy adults [47]. The recto- anal inhibitory reflex (RAIR) will also be elicited by a 50-ml rapid inflation (if necessary in 50-ml aliquots up to 150 ml)
3. Fixed volume (50 ml) water-filled rectal balloon expulsion test [42, 43, 48, 49] in the seated position on a commode. Abnormal expulsion is defined as abnormal if failure to expel with a 1-min effort for men and 1.5 min for women [50]
4. Whole gut transit study using serial (different shaped) radio-opaque markers over 3 days with a single plain radiograph at 120 h [51, 52]

Note: INVEST procedures conducted prior to recruit- ment to the study (i.e. within the past 12 months) may be done using locally available devices and methods.

All patients will undergo TAI therapy irrespective of INVEST results, and will be followed up in the same way. The purpose of INVEST in this study is to identify whether certain radio-physiological results correlate with treatment response, i.e. can we predict likelihood of benefitting from irrigation based on pretreatment inves- tigations. Balloon sensory testing in combination with patient-reported urge to defaecate will be analysed as co- variates to determine whether such a relationship is present.

Concomitant medications

It is inevitable that patients will seek recourse to laxa- tives and other dietary supplements during the course of the programme. Experience shows that complete prohib- ition can lead to unreported laxative use, which might confound findings. Although we will strongly discourage ad libitum medication usage and specify a defined break- through regimen, we will record cotreatment with suffi- cient fidelity and integrity to enable use as covariates in analyses using a specific patient journal for this purpose (see 'Standardised outcome framework'). A concomitant medications list, including a shortlist of contributory or confounding medications, will be used to filtre on data entry. Patients using one system in the medium/long term may wish to revert to the other system or pause treatment for a short period (for example, while going on holiday) for practical reasons. This is permitted but must be recorded in the concomitant medications log. This will not be considered as switching or ending treat- ments as it is only a short-term measure.

Criteria for discontinuation

The interventions proposed are well-established in current clinical practice. There are no defined criteria for discontinuation; however, clinicians may withdraw treatment where they have therapeutic or safety con-cerns, consistent with routine care. Patients may choose to discontinue treatment at any point and return to rou- tine clinical care.

Procedure for collecting data including Case Report Forms (CRFs) and storage

The data collected for the trial will be a mixture of routinely collected data, verifiable against the medical record and patient-reported outcome (PRO) or question- naire data, collected directly to CRF.

Each recruiting site will be required to keep accurate and verifiable source notes in the medical record rele- vant to each study participant's inclusion and continued participation in the study. Data will be collected, trans- ferred and stored in accordance with GCP guidelines and data protection requirements. The PCTU standard operating procedures (SOPs) and study data manage- ment plan will define the exact process of data collec- tion, transfer and storage and control of study data.

A secure online OpenClinica trial database will be pro- vided by the PCTU to enable remote data entry at sites where this is feasible. This database will provide built-in data-validation checks with quality control (QC) checks performed by checking a predefined percentage of CRF data against data entered into the database. In addition, on-site monitoring will enable source document verifica- tion (SDV) of records.

Patient-reported outcome measures (PROMs), includ- ing questionnaires and diaries, may be collected directly to the eCRF using a secure and controlled REDCap database. An automated email reminder will be sent to participants to remind them to complete the question-naires and diaries every 12 weeks. Alternatively, partici- pants can complete paper questionnaires and diaries to be entered by the central study team.

All patient-identifiable data, such as Consent Forms, screening and identification logs will be stored in the in- vestigator site files in secure locked cabinets and/or of-fices, accessible only to delegated members

of the study team. Secure methods of data transfer will be used to re- turn CRFs to the coordinating site for centralised data entry, monitoring, QC in compliance with GCP. A copy of the CRF will be held at the site in accordance with GCP.

Follow-up procedures

The study duration allows for follow-up to a maximum of 12 months with data collection at 3, 6 and 12 months post initiation of therapy. Primary outcome data will be collected at 3 months. Each participant will have a minimum of 3, 6 and 12 months' follow-up data for collecting the pri- mary and secondary outcomes. In addition, PAC-SYM, PAC-QOL and EQ-5D-5 L and EQ-VAS will be recorded at the 1-month visit; this is to capture information on early nonresponders and to better understand and characterise this group of patients. Participants will leave the study and return to 'routine clinical care' as determined within their local NHS institution (or be recruited to subsequent trials). Alternatively, they may wish to proceed to enrollment in the next WP (study 3 – Laparoscopic Ventral Mesh Rectopexy) within the CapaCiTY programme.

The following data will be collected at each visit up to 12 months

- Validated symptom and QOL questionnaires (PAC-SYM and PAC-QOL). Validated generic QOL questionnaires: EQ-5D-5 L descriptive system and EQ-VAS. Note: EQ-VAS has a standard deviation (SD) of approximately 30 points: a 10% difference in VAS deemed clinically significant can be detected with the large sample sizes proposed
- Patient Health Questionnaire-9 (PHQ-9) [53–55]
- Generalised Anxiety Disorder Questionnaire (GAD-7) [56]
- Depression, anxiety and somatisation modules of the Patient Health Questionnaire [53–56] and the Illness Perception Questionnaire [57]
- Global patient satisfaction/improvement score (VAS) and whether they would recommend each treatment experienced to other patients
- Potentially modifiable cognitive and behavioural psychological variables shown to predict onset and perpetuation of other functional bowel symptoms: negative perfectionism, avoidant and 'all or nothing' behaviour subscales of the Behavioural Response to illness Questionnaire (CC-BRQ), and the Brief Illness Perception Questionnaire BIPQ (CC)
- A 2-week Patient Diary (for 2 weeks prior to each assessment at 3, 6 and 12 months) to record bowel frequency and whether each evacuation was spontaneous (no use of laxatives) and/or complete; the patient journal will also capture concurrent medication, health contacts, and time away from normal activities (including work). Patients will be contacted by telephone to remind them to start the diary. If a patients forget to do this, then it is acceptable for them to start recording the diary on the day that they are seen in clinic and for this to be collected 2 weeks later
- Resource use data (using patient journals as a prompt and including concomitant medication use)
- Irrigation Diary to record frequency and volume of irrigation and any AEs

Laboratory assessments

Serum or urine pregnancy testing may be performed as per standard care for any women of equivocal status undergoing radiological assessments (INVEST).

Radiology assessments

The whole gut transit study usually (90% patients) in- volves the use of a single, plain abdominal radiograph (in 10% patients, a maximum of two may be required to image the whole abdomen and pelvis). This procedure forms part of routine clinical care for patients with CC at many NHS centres. All practitioners (radiologists, radiographers, etc.) directing these studies will hold ap- propriate IR(ME)R certification.

Participant withdrawal (including data collection/ retention for withdrawn participants)

Individual participants will be able to withdraw from treat- ment at any time by notifying health care professionals in- volved with the study, and return to routine care without prejudice. Data will be retained for analysis from all partic- ipants after the point of consent and recruitment.

Criteria for withdrawal from treatment:

Participant develops any of the following exclusion criteria

- Participant becomes pregnant or intends to become pregnant (only in baseline and intervention phases)
- Participant is subsequently diagnosed with a proven cause for secondary constipation, e.g. Parkinson's disease or bowel obstruction
- Participant requires new medication with proven effects on bowel function, e.g. opioids
- Participant develops significant intercurrent illness precluding participation
- Participant requires surgery or other intervention (other than minor ops) during treatment or follow-up phase
- Participant develops acute psychological problem causing safety concern
- Adverse events secondary to therapy (bleeding, anal fissure, ulceration, pain, bowel perforation) – relative indications for withdrawal depending on the views of the patient and physician. (Note: bowel perforation is an absolute indication for withdrawal)
- Elective withdrawal

Loss to follow-up (no further interventions or follow-up data collected)

- During follow-up (up to 12 months), participants may be withdrawn from the trial if they become lost to follow-up (LTFU) after at least three failed attempts by research staff to make contact via two different methods (e.g. telephone and letter)
- Participant chooses to withdraw and does not wish to participate in follow-up data collection
- Death or significant incapacity making follow-up data collection impossible

End of study definition

The end of study is defined as the last patient last visit. The sponsor, REC and local R&D departments will be informed of end of study and site closure and archiving procedures initiated.

Criteria for early termination

If the Data Monitoring and Ethics Committee (DMEC), Programme Steering Committee (PSC), Research Ethics Committee (REC) or sponsor determine that it is within the best interests of the participants or trial to terminate the study, written notification will be given to the chief investigator (CI). This may be due to, but not limited to: serious safety concerns, serious breaches, acts of fraud, critical findings or persistent noncompliance that nega- tively affects patient safety or data integrity. If the study is terminated participants will be returned to the NHS normal follow-up and routine care.

Qualitative interviews

The purpose of this qualitative enquiry is to complement the quantitative study of TAI. A phenomenological methodology will be employed and qualitative data will be collected in parallel with the quantitative study. Par- ticipants will be recruited separately from the quantita- tive study, with separate PISs and consent processes.

Sampling

A purposive sample of approximately 35 patients will be invited to interview upon

completion of irrigation training and then again at 6 months. Participants do not have to participate in both sets of interviews; a separate set of patients can be interviewed at 6 months. Recruitment can be extended if data satur- ation is not accomplished by the 35th patient. Data saturation is defined as the point at which no new or relevant themes emerge. Inclusion and exclusion cri- teria are as above. Participants will be selected from a sampling grid of potential interviewees to reflect a range of ages, geographical locations and, where pos- sible, other pertinent attributes such as ethnicity and gender. An approximately equal number of patients will be selected from each trial arm as follows:

- Seventeen patients undergoing low-volume anal irrigation and 18 patients undergoing high-volume irrigation and including those who discontinue early (before 3 months), later (3–5 months), those who continue with their allocated treatment, and those who switch
- In addition, approximately 10 health professionals involved in delivering the treatment will be interviewed. These health care professionals will be evenly distributed across participating centres

Data collection

All participants will be told that they might be invited for interview when they are initially informed about the study. Participants will be contacted by a member of the clinical team and if interested in being inter- viewed a separate PIS will be provided. Participants will be offered a semistructured interview in a clinic room or in their own home according to their prefer- ence, and will be offered a chaperone to be present if they would prefer. Professionals will be interviewed in a clinic setting. Following written consent, the inter- views will be recorded on a digital dictaphone and transcribed into a pseudonymised (alphanumeric code) text document. Interviews will be conducted by an ex- perienced qualitative researcher working within the wider CapaCiTY research programme. A clinical re- search fellow at UHND and/or a health research methodologist at Durham University will conduct in- terviews recruited from the Durham site.

Interviews will explore health professionals' and partic- ipants' experiences of recruitment, individual interven- tions, their training and delivery, and patients' views about outcome measures. A topic guide for each of the interviews and focus groups, informed by the existing literature and our patient advisors, will be developed.

Timing

Patients will be invited to one-to-one interviews on completion of training and will be interviewed a max- imum of 4 weeks after training to maximise recall. Pa- tients will be recalled up to 6 months after training and offered an interview. The patients interviewed at base- line do not have to be the same as those interviewed up to 6 months. Interviews will be conducted throughout to capture relatively early and later experiences and percep- tions of the interventions.

Analysis

Interviews will be digitally recorded, anonymised, transcribed verbatim and analysed using a thematic analysis and NVivo8 software (QSR International Ltd., Warrington, UK) for data management. Data analysis will be developed as outlined by Fereday and Muir- Cochrane [58] in the first instance by mapping key con- cepts derived from the transcripts ('charting') and extract- ing emergent themes from the transcripts. Professor Norton will coordinate and conduct analysis, while for the purposes of Christopher Emmett's MD, independent ana- lysis will be conducted by CE and Dr. Helen Close. Emer- gent themes, together with captured observational data, will form the basis of analytical interpretation. Data will be handled in a confidential manner at all times, and only transferred on encrypted media or via secure electronic transfer.

Statistical considerations

Sample size

PAC-QOL is a 28-item disease-specific measure, with each item scored 0–4, and providing an aggregate score 0– [34]. Superiority of either low-volume or high-volume anal irrigation is demonstrated by a 10% scale difference (or more), or 0.4, with a variance estimate conservatively set at SD = 1 from the published medical literature [59]. To detect an effect size of 0.4 (mean/ SD = 0.4) between the two groups with 90% power and 5% significance at 3 months requires 133 patients per arm, and 266 total. Allowing for an anticipated 10% loss to follow-up (LTFU), then 300 patients will be recruited.

Clinical outcomes

A full analysis plan will be signed off before allocation codes are made available to the statistician. The codes will not indicate which treatment arm is which so that as far as possible the statistician will remain blind to al- location throughout the analysis. All analyses will be by the intention-to-treat principle. The primary outcome will be PAC-QOL as a continuous variable, analysed at 3 months while the quarantine period is in effect. The proportion of patients continuing with the initial therapy system will be recorded, and the PAC-QOL scores will be analysed using a linear mixed model with a random effect for centre and fixed effects for intervention, trial stratification variables (participants are stratified by sex and women by centre) and baseline PAC-QOL. Second- ary outcomes will be analysed using the principles out- lined above for the primary outcome.

Exploratory modelling will be conducted for baseline characteristics: measures of chronic pain, autonomic, joint hypermobility, cognitive, behavioural and mood variables share a common hypothesis that they are detri- mental to the success of all treatments, i.e. they perpetu- ate illness in spite of therapy. We will investigate a maximum of three interactions between treatment and baseline characteristics. These will be described in the SAP a priori. Appropriate regression models, including interaction terms, will be developed to determine the in- fluence of these pretreatment characteristics on the suc- cess of treatments in all WPs.

Life table data for any irrigation will be presented by initial therapy and for specific therapy from date of com- mencement. Survival analysis will be presented using Kaplan-Maier analysis and adjusted using Cox regres- sion. Exploratory analysis will be considered to identify characteristics of subgroups with greatest persistent benefit from irrigation. These will be described in the SAP a priori.

Analysis will be performed using proprietary software, (Stata Corp., College Station, TX, USA). $P < 0.05$ will be

taken to indicate statistical significance. No analyses will be conducted until an analysis plan has been written, reviewed by an independent statistician and signed off.

Multiple imputation will be considered to address missing covariate values. Details of any imputation to be performed will be described in the SAP which will be finalised after initial checks on completeness of the data but before performing any analysis or unblinding of the data.

Health economic outcomes

The patient journal will facilitate the capture of health economic data which will be recorded on the CRF at each visit. This will be combined with the initial cost of the device and weekly consumables.

Within-trial stochastic analysis will compare the cost/ success and cost/quality-adjusted life year (QALY) of anal irrigation. Patient-level cost-effectiveness analysis will use standard bootstrapping methods to generate cost-effectiveness acceptability curves exploring value for money. Within-cohort combined stochastic/probabilistic epidemiological models will be used to assess irrigation and surgery options, exploring relative effectiveness and cost-effectiveness according to patient characteristics.

Cost-effectiveness models that extrapolate beyond 3–6 months' duration are problematic in adult constipation, as subsequent care and outcomes are contingent upon subsequent care received and the underlying disease process. However, the programme of WPs, and inclusion of time to failure data capture, provides a unique oppor- tunity to construct probabilistic models exploring opti- mal pathways from effectiveness and cost-effectiveness perspectives.

Since patients will (within the CapaCiTY programme) be followed along a pathway that includes a series of steps of care, it will be possible to construct costs and outcomes for a range of patient pathways providing comparative longer-term cost-effectiveness estimates. Patient-level data from recruitment through the various WPs will be used to construct pragmatic, probabilistic models to explore optimal pathways from effectiveness and cost-effectiveness perspectives.

Analyses from NHS and societal perspectives will be supported by recording relevant resource use during each WP, and a common panel of outcomes. Adjustment for time preference will be at the socially accepted rate for cost-effectiveness analyses (currently 3.5%/annum for costs and benefits).

Data analysis for MD thesis

The study will form the basis of a thesis for an MD at Durham University by a research fellow (Christopher Emmett) at University Hospital of North Durham (UHND). Patients recruited at UHND and the Royal Victoria Infirmary, Newcastle upon Tyne up to 1 October 2016 (estimated 50 patients) will be analysed in this thesis, including those recruited to the qualitative arm of the study at this site. These patients will have a minimum of 3 months of study data. The release of data from the UHND and Newcastle sites for this purpose has been approved by the chief investigator (CI) on the condition that it may be used for thesis examination but is not published or made publically available until the CapaCiTY programme results are published in full. The qualitative data from the Durham site may be published separately as agreed.

Laboratories (if applicable)

Serum pregnancy testing will be performed by local NHS biochemistry laboratories.

Products, devices, techniques and tools

Devices

There are no investigative medicinal products or investi- gative devices under study. The following is a list of all devices routinely used in clinical care and none are spe- cific to the research itself. All are CE-marked and approved for use in the UK.

1. Disposable proctoscope (supplier as local NHS practice). This will be commonly be used as part of clinical examination at baseline and is also used to introduce balloon catheters into the rectum during INVEST
2. High-resolution anorectal manometry (HRAM system + Unisensor HRAM catheter (200 uses) and balloons, software, cables, calibration kit, isolation transformer and laptop. Insertion and use are outlined under the 'Interventions' section (equipment provided at study outset)
3. Standard anorectal manometry catheter, balloons, software, cables, calibration kit and associated equipment; standard equipment in many NHS centres for performing anorectal physiology. Can be used as an alternative where high-resolution manometry is not available (part of INVEST – see above)
4. Balloon catheters for balloon expulsion test (part of INVEST – see above)
5. Radio-opaque markers for colonic transit study: various suppliers (part of INVEST – see above)
6. Standard departmental X-ray equipment (part of INVEST – see above)
7. Peristeen™ anal irrigation system (Coloplast), Qufora® Balloon™/Qufora Toilet anal irrigation systems (MBH-International): established anal irrigation systems available on prescription in NHS practice. Other systems with the same mechanism of action may also be used (dependent on local funding and prescribing arrangements)
8. Qufora® Mini anal irrigation system (MBH-International): established anal irrigation system available on prescription in NHS practice

All devices are maintained, calibrated and serviced ac- cording to standard NHS policies and procedures ac- cording to manufacturer's guidance. Training on devices is provided by the supplier's representatives. Additional study SOPs and training will be provided to ensure standardisation across sites, but will be in line with current NHS standard practice.

Data collection tools

The permissions/licenses to use the below instruments have been sought on the understanding that sites are permitted to utilise these within this study only, they will be provided to sites as part of the CRF for the study:

- PAC-QOL score: from MAPI Research Trust
- PAC-SYM score: from MAPI ResearchTrust
- EQ-5D-5 L: from EuroQol

The below-listed questionnaire-based tools are free to use within the public domain and will be provided to sites as part of the CRFs for the study.

- Depression, anxiety and somatisation modules of the Patient Health Questionnaire
- Illness Perception Questionnaire
- Composite Rome III/Cleveland Clinic Constipation Questionnaire: free to use
- Brief, chronic pain, autonomic and joint hypermobility: free to use
- Negative perfectionism
- Avoidant and 'all or nothing' behaviour subscales of the Behavioural Response to Illness Questionnaire

Safety reporting

Adverse events (AEs)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, includ- ing occurrences which are not necessarily caused by, or related to, that intervention. An AE can, therefore, be any unfavourable and unintended sign (including an ab- normal laboratory finding), symptom or disease tempor- arily associated with study activities.

Notification and reporting adverse events or reactions

The anal irrigation systems are in widespread and estab- lished clinical use throughout the NHS with known AEs occurring (22%) being mostly low grade and reversible. All trial interventions are as per the standard care

provided within the NHS for CC. Related AEs will be re- corded on the CRF. Serious adverse events (SAEs) will be recorded on the CRF and in the medical notes to en- able assessment and reporting in line with sponsor and regulatory requirements. Causality will be at the discre- tion of the health care provider (e.g. research nurse, physiotherapist, PI or delegated member of team). These will be assessed as outlined below.

Trial participants will be advised to seek medical sup- port from their GP for any unrelated signs, symptoms or disease or aggravation of underlying symptoms.

Serious adverse event (SAE)

In other research other than CTIMPs, a SAE is defined as an untoward occurrence that:

1. Results in death
2. Is life-threatening.
3. Requires hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Consists of a congenital anomaly or birth defect, or
6. Is otherwise considered medically significant by the investigator

An SAE occurring to a research participant should be reported to the sponsor and Main Research Ethics Committee (MREC) where, in the opinion of the CI, the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence (see Additional file 3)

Notification and reporting of SAEs

Serious adverse events (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the spon- sor within 24 h of learning of the event and to the MREC within 15 days in line with the required time-frame. For further guidance on this matter, please refer to the HRA website and Joint Research Management Office (JRMO) SOPs.

Expected SAEs

The following SAEs are expected to occur rarely in this patient population and will not be reported:

- Hospital admission for exacerbation of constipation symptoms including impaction
- Hospital admission for unrelated elective surgical procedures or accidental injury

Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the re- sponsibility of the CI to inform the sponsor and the MREC (via telephone) of this event immediately.

The CI has an obligation to inform both the MREC in writing within 3 days, in the form of a substantial amendment. The sponsor, JRMO, must be sent a copy of the correspondence with regards to this matter. For fur- ther guidance on this matter, please refer to the HRA website and JRMO SOPs.

Annual safety reporting

The CI will send the Annual Progress Report to the MREC using the HRA template (the anniversary date is the date on the MREC 'favourable opinion' letter from the MREC) and to the sponsor. Please see the HRA web- site and JRMO SOP for further information.

Overview of the safety reporting responsibilities

The CI/PI has the overall responsibility for oversight of safety reporting. The CI/PI also has a duty to ensure that safety monitoring and reporting is conducted in accord- ance with the sponsor's requirements.

Monitoring and auditing

The PCTU quality assurance (QA) manager will conduct a study risk assessment in collaboration with the CI. Based on the risk assessment, an appropriate study mon- itoring and auditing plan will be produced according to PCTU SOPs. This monitoring plan will be authorised by the sponsor before implementation. Any changes to the monitoring plan must be agreed by the PCTU QA man- ager and the sponsor.

Audit definition:

'A systematic and independent examination of trial- related activities and documents to determine whether the evaluated trial-related activities we reconducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's SOPs, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).'

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.

2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations
4. Projects may be selected at random. The Department of Health states that trusts should be auditing a minimum of 10% of all research projects
5. Projects may be randomly selected for audit by an external organisation

Internal audits may be conducted by a sponsor's or a funder's representative according to JRMO/NIHR SOPs.

Safety considerations

Patients recruited who have not had previous INVEST procedures conducted within the last 12 months will undergo a radiological procedure (whole gut transit) using ionising radiation as outlined above. The average dose of this procedure (approximately 0.1 mSv) is equivalent to about 2.5 weeks' annual background radi- ation dose from living in the UK Further, these investiga- tions would be carried out in routine clinical practice in many centres for patients at the same point as recruit- ment to this study.

Regarding the intervention, anal irrigation is associated with a very low incidence of bowel perforation, as well as other side effects (bleeding, pain, ulceration, painful haemorrhoids, anal fissure). Patients will be counselled regarding these risks as part of the process of informed consent. In addition, they will be trained in the correct use of the device prior to commencing therapy. All re- lated AEs and all SAEs will be recorded and therapy sus- pended while these are investigated.

Trial committees

The project will be under the auspices of the CI and the PCTU. The project will be overseen by a Programme Steering Committee (PSC).

The composition and responsibilities of the PSC will comply with the NIHR guidance and PCTU SOP on Trial Oversight Committees. The role of the PSC is to provide overall supervision of the study on behalf of the sponsor and funder to ensure that study is conducted in accordance with the principles of Good Clinical Practice (GCP) relevant regulations.

The responsibilities of the PSC will include:

- Ensuring that the views of users and carers are taken into consideration
- Advising on the trial protocol
- Advising on changes in the protocol based on considerations of feasibility and practicability

- Assisting in resolving problems brought to it by the Programme Management Group (PMG)
- Monitoring the progress of the trial and adherence to protocol and milestones
- Considering new information of relevance from other sources
- Considering and acting on the recommendations of the Data Monitoring Committee (DMC), sponsor and/or MREC
- Review initial reports and papers for publication

The PSC will meet to review the protocol before the start of the programme and then soon after the first par- ticipants are recruited and either meet or teleconference every 6 months thereafter throughout the lifetime of the programme.

Representatives of the trial sponsor and the funder will be invited to attend.

A PMG made up of core staff from the coordinating centres and the PCTU will meet monthly initially during study set-up and then less frequently, every 2 months. The PMG will be responsible for day-to-day project delivery across participating centres, and will report to the PSC.

An independent Data Monitoring and Ethics Committee (DMEC) will be convened. The DMEC will meet at least 4 weeks prior to the PSC to enable recommendations to be fed forward.

A DAMOCLES charter will be adopted, and the pro- ject team will provide the DMEC with a comprehensive report, the content of which should be agreed in ad- vance by the chair of the DMEC and follow guidelines set out in the charter.

A Constipation Research Advisory Group (CRAG) will be formed as part of a well-developed Patient and Public Involvement (PPI) strategy at QMUL. This advisory group will comprise eight patients and two lay members derived from London and Durham. This group will have geographical diversity (north and south) and a disease-appropriate demographic (eight women, two men). The CRAG will be involved in:

- Review of PISs, booklets, diaries and advertising/ marketing materials
- Project management by representation on the PSC
- Parallel qualitative analysis
- Dissemination of results and lay summaries
- Presentations at local research events
- Patient focus groups and workshops

Project management

Local coordination

Each participating centre will identify a site-specific PI who will nominate a local contact for that centre (this may be themselves). The PI and local contact will:

- Be familiar with the trial
- Liaise with the PCTU and the PMG
- Ensure that all staff involved in the trial are informed about the trial and have received requisite training
- Ensure that mechanisms for recruitment of eligible participants, including the availability of participant information and data collection tools, are in place; monitor their effectiveness and discuss the reasons for nonrecruitment with relevant staff
- Ensure that site staff collect necessary trial data and perform quality checks
- Notify the CI of any SAE's
- Make data available for verification, audit and inspection processes as necessary, and respond to requests for documentation and data required for centralised monitoring
- Ensure that the confidentiality of all information about trial participants is respected by all persons

Site initiation and training

A central study launch meeting and/or site initiation will be conducted with each site. This will include training in the trial protocol and SOPs, such as data collection, randomisation and taking informed consent. Evidence of appropriate training, local approvals and essential docu- mentation will be required before participants being enrolled at each site. Training will be documented on training logs.

Project timetable, milestones and projected recruitment

The PMG will be responsible for monitoring adherence to the study timelines and expected recruitment rates. Regular reports will be produced to enable deviations from the project plan to be identified and contingencies planned, discussed and executed in a timely fashion.

Projected recruitment dates are:

1 Aug 2015: first participant
31 Apr 2016: 100 participants
30 Nov 2016: 200 participants
30 Jun 2017: 300 participants
30 Oct 2017: last patient intervention
31 Apr 2018: 3-month primary endpoint
31 Oct 2018: 12-month secondary endpoint

Discussion

The CapaCiTY 02 study is a large and potentially very rich study in terms of hypothesis-testing and generating robust evidence. As previously noted, its primary aim of establishing superiority of one system of irrigation over another will provide valuable information that can be used to guide the choice of therapy in patients with CC. Additionally, the study aims to explore health economic

outcomes, and will also evaluate the association between pretreatment baseline characteristics (e.g. psychological profile, joint hypermobility, colonic transit, anorectal physiology) and treatment success. Alongside these ele- ments, a qualitative component of the study will explore the lived experiences of patients and health care profes- sionals who are using irrigation, or training patients in its use.

The multisite nature of the study, along with the broad range of outcome measures being employed, could po- tentially lead to several practical challenges in imple- menting the study protocol. Attempts have been made to anticipate and address these before commencing study recruitment. Prestudy site feasibility questionnaires were circulated to all sites wishing to participate, and these were used to identify the key components of irriga- tion training and treatment at each site. The training process described in this protocol aims to be as applic- able as possible to as broad a range of sites as feasible, without causing the study sites to make significant alter- ations to their standard practice.

The protocol also aims to be flexible as regards pre- treatment investigations. These have been limited to anorectal physiology and a transit study (see section above: 'INVEST'). It was felt that these provided im- portant information necessary for characterising pa- tients before starting treatment, thereby allowing analysis of the relationship between pretreatment characteristics and treatment success. It was decided, as few sites had access to HRAM, that standard man- ometry was sufficient for the purposes of this study. This increased participation by allowing sites not in possession of the necessary high- resolution equipment to still recruit to the study.

It is recognised that the study design has several limi- tations. From a methodological perspective, the fact that neither participant nor assessor blinding was feasible (due to the nature of the treatment and the nature of the outcome data being collected), leads to the possibil- ity of performance bias and reporting bias, as both participants and assessors will (consciously or uncon- sciously) have particular preconceived ideas about the likely efficacy of each system. Attempts have been made, from a methodological and operational perspective, to limit the impact of this. The fact that every patient re- ceives treatment is important, as it is a reasonable as- sumption that the placebo effect for each system is similar, thereby meaning that any observed difference between systems is a genuine one. Additionally, the op- tion of switching systems after 3 months is designed to allow participants who have not had success with their original system to try the other one. This means that pa- tients do not spend too long on ineffective treatment, and also allows longer-term data (more than 3 months)

to evaluate the effectiveness of the treatment as a whole in the long term.

As can be seen from the 'Trial status' section below, recruitment nationally has fallen below the planned rate of recruitment. Several reasons for low recruitment have been identified through discussions with participating sites; these are mainly the result of variation in local practice (making the protocol difficult to implement), as well as service pressures and the pressure on research teams from doing more than one study in the CapaCiTY programme. This highlights the difficulties in imple- menting multisite studies, and even though attempts were made before study commencement to ensure suffi- cient flexibility in the proposed study design, problems have nonetheless been encountered.

Since recruitment has opened, recruitment rates at each study site are monitored and monthly meetings are held to discuss progress and to identify problems at an early stage. Teleconferences have been held with recruit- ing sites in order to discuss and resolve barriers to recruitment.

Trial status

As of 31 August 2016, the study has seven sites open to recruitment. The first patient was enrolled on 15 October 2015. Currently, 39 patients have been screened and 22 randomised. Of these, two have withdrawn (elective withdrawal – no reason given).

Additional files

Additional file 1: CapaCiTY programme overview. (DOCX 152 kb)

Additional file 2: SPIRIT Checklist. (DOCX 66 kb)

Additional file 3: Communication organogram for reporting serious adverse events (SAEs). (DOCX 52 kb)

Committee; QA: Quality assurance; QC: Quality control; QOL: Quality of life; RAIR: Recto-anal Inhibitory Reflex; RCT: Randomised controlled trial;

REC: Research Ethics Committee; SAE: Serious adverse event; SAP: Statistical analysis plan; SD: Standard deviation; SDV: Source document verification; SOP: Standard operating procedure; TAI: Trans-anal irrigation; TDS: Three times per day; VAS: Visual Analogue Scale; WP: Work package signature page

Acknowledgements

Not applicable

Funding

The study is being financed as part of an NIHR PGfAR award RP-PG-0612-20001: £1,971,934. Additional resource will be provided via host CLRNs. The calculation of all costs and contracting has been performed in conjunction with the sponsor.

Indemnity

Queen Mary University London has agreed to act as study sponsor. Insurance and indemnity will be provided by the sponsor.

Availability of data and materials

The trial data will be made available to suitably qualified members of the research team, study monitors and auditors, the sponsor, the REC and regulatory authorities as far as required by law. The participants will not be identifiable with regards to any future publications relating to this study. When the research trial is complete, it is a requirement of the Research Governance Framework and trust policy that the records (including paper records, digital records and audio files) are kept for a further 20 years. For trials involving BH Trust patients, undertaken by trust staff, or sponsored by BH or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre.

Each site will be required to archive local site files and patient-identifiable information, such as Consent Forms and screening logs, for a period of

20 years. At the end of the 20-year retention period, permission should be obtained in writing from the sponsor prior to destruction of this material.

Authors' contributions

CE contributed to study design, protocol development and manuscript preparation. HC assisted with study design and protocol development, as well as writing the 'Qualitative methods' section. JM and SE oversaw protocol development and trial design, and codescribed the statistical

methods. JM is the health economics lead. NS and ST assisted with trial

design and protocol development. CN assisted with trial design and protocol development and is PI for the qualitative arm of the study. CK conceived the trial, secured NIHR funding, and is CI to the CapaCiTY programme. YY oversaw, and contributed to, the study design and protocol development, and is PI for the CapaCiTY 02 study. All authors have read and approved the final manuscript.

Abbreviations

AE: Adverse event; BD: Twice per day; BIPQ: Brief Illness Perception Questionnaire; BNF: *British National Formulary*; CC: Chronic constipation; CI: Chief investigator; CPCPH: Centre for Primary Care and Public Health; CRF: Case Report Form; DMEC: Data Monitoring and Ethics Committee; EC: European Commission; EQ-5D: EuroQol Health Outcome measure; EQ-VAS: EuroQol Visual Analogue Scale; FDD: Functional defaecation disorder; GAD-7: Generalised Anxiety Disorder Questionnaire; GAfREC: Governance Arrangements for NHS Research Ethics Committees; HRA: Health Research

Authority; HT: Habit training; HTBF: Habit training incorporating direct visual biofeedback; INVEST: Standard panel of radio-physiological tests of colonic and anorectal function; JRMO: Joint Research Management Office; LTF: Lost to follow-up; NDUHT: North Durham University Hospital Trust; NHS

R&D: National Health Service Research & Development; NHS REC: National Health Service Research Ethics Committee; PAC-QOL: Patient Assessment of Constipation Quality of Life questionnaire; PAC-SYM: Patient Assessment of Constipation Symptoms Questionnaire; PCSG: Primary Care Society for Gastroenterology; PCTU: Pragmatic Clinical Trials Unit; PHQ-9: Patient Health Questionnaire – 9; PI: Principal investigator; PIS: Participant Information Sheet; PMG: Programme Management Group; PPIG: Patient and Public Involvement Group; PRO: Patient-reported outcome; PSC: Programme Steering

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

The CI will coordinate dissemination of data from this trial. All publications using data from this trial to undertake original analyses will be submitted to the PSC for review before release. To safeguard the scientific integrity of the trial, data will not be presented in public before the main results are published without the prior consent of the PSC. The success of the trial

depends on a large number of clinicians. For this reason, credit for the results will not be given to the committees or central organisers, but to all who have collaborated and participated in the trial. Acknowledgement will include all local coordinators and collaborators, members of the trial committees, the PCTU and trial staff. All contributors to the trial will be listed at the end of the report, with their contribution to the trial identified. Those responsible for other publications reporting specific aspects of the trial may wish to utilise a different authorship model, such as '[name], [name] and [name] on behalf of the collaborative Group'. Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the PSC.

A lay summary of the final results of the trial will be made available for participants on the Bowel and Cancer Research charity website with a link to the full paper.

Ethics approval and consent to participate

General

This study (study 2 of the CapaCiTY programme) will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

Ethics approval for the whole CapaCiTY programme (studies 1 to 3) has been sought from one of the London NRECs (London City and East). Within the programme, the three studies will be distinct studies and protocols, and thus consented separately. This is necessary to limit patient information which would otherwise be over-burdensome. The REC reference and IRAS number for CapaCiTY 02 are given below.

REC Reference 15/LO/0732.
IRAS 172401.

Informed consent procedures

Written informed consent will be obtained at visit 1 from research participants by an appropriately trained and delegated researcher in a face-to-face setting in clinic. For study Consent Forms, see Additional files 4 (quantitative study) and 5 (qualitative study).

Ethical considerations

The protocol has been reviewed by Professor Richard Ashcroft, Professor of Medical Ethics and Law at QMUL. Important considerations that have informed pragmatic design include (a) *limitation of intimate examinations*: to one time point (not repeated if performed before recruitment), (b) *timings of outcomes*: within this study outcomes will be undertaken at 3, 6 and

12 months from the commencement of the first treatment for all patients, with additional recording of key outcome measures (PAC-QOL, PAC-SYM,

EQ-5D-5 L and EQ-VAS, Irrigation Journal and Patient Journal). For this period of 6 months, patients will not progress to further WPs thus preventing outcome 'contamination'. Additionally there will be a 3-month 'quarantine' from switching irrigation therapy. These delays are akin to that in usual NHS care, during which general supportive care will be provided. This proposed limitations at 3 and 6 months confers no disadvantage and may even represent an acceleration of treatment progression. Ethically, this is viewed as a reasonable trade-off for the commitment to the research programme,

(c) *recruitment and consent*: study 2 represents one of the three studies incorporated in the NIHR-funded CapaCiTY programme. Although patients may move sequentially through treatments (and, therefore, studies) during the programme course, study 2 will be consented as a distinct single entity and (d) *qualitative interviews*: these will be in-depth interviews conducted one-on-one (plus a chaperone if requested by the patient) and, therefore, there are potential risks to the safety of the interviewer. Also, the thorough nature of the interviews could lead to psychological distress for the participant. It is, therefore, necessary to identify patients who would be at especially high risk in either of these ways and to exclude them from the study. Baseline assessment would identify and enable exclusion of individuals with pre-existing psychiatric disorders or a history of high-risk behaviours (self-harm, drug and alcohol addiction). Counselling and support from health care professionals involved in patient care will be available for any subject experiencing untoward distress.

Protocol amendments

In the event of a protocol amendment being required, details of the proposed amendment will be submitted to the sponsor initially for review and authorisation of submission as either a minor or substantial amendment. For substantial amendments, an IRAS amendment form, cover letter and all

amended documents (along with a summary of changes) will be submitted to the REC for approval. Once approved, details of the amendments and any action required will be circulated to each participating site PI and local R&D/ CRN. The CI will submit all nonsubstantial/minor amendments to HRA for classification according to HRA guidelines, the results of which will be provided to participating site PI, R&D and CRN as required.

Confidentiality

Information related to participants should be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of REC approval.

Identifiable information to be collected from the participants includes, full name, date of birth and hospital number and contact details at screening. This information will be used to contact participants but will not leave the study site without prior consent and approvals. All CRFs will be pseudonymised. The participant's GP will be informed of their participation in the study.

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