RANDOMISED TRIAL OF HABIT TRAINING VS. HABIT TRAINING WITH DIRECT VISUAL BIOFEEDBACK IN ADULTS WITH CHRONIC CONSTIPATION

Short Title/Acronym Chronic Constipation Treatment pathwaY, study 1 CapaCiTY study 1

Sponsor Queen Mary, University of London

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- Norfolk and Norwich University Hospitals NHS Foundation Trust [Spearman]
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- Dorset County Hospital NHS Foundation Trust [Lamparelli]
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- Professor Christine Norton, joint lead in study01 and lead in all qualitative research, Northwest NHS
- Ms Deborah Gilbert, public representative on programme steering committee, Bowel and Cancer Research charity
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Central facilities

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<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>ASR</td>
<td>Annual Safety Report</td>
</tr>
<tr>
<td>B IPQ</td>
<td>Brief Illness Perception Questionnaire</td>
</tr>
<tr>
<td>CC</td>
<td>Chronic constipation</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CPCPH</td>
<td>Centre for Primary Care and Public Health</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DMEC</td>
<td>Data Monitoring and Ethics Committee</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQol Health Outcome measure</td>
</tr>
<tr>
<td>EQ-VAS</td>
<td>EuroQol Visual Analogue Scale</td>
</tr>
<tr>
<td>FDD</td>
<td>Functional defaecation disorder</td>
</tr>
<tr>
<td>GAD7</td>
<td>Generalized anxiety disorder questionnaire</td>
</tr>
<tr>
<td>GAfREC</td>
<td>Governance Arrangements for NHS Research Ethics Committees</td>
</tr>
<tr>
<td>HT</td>
<td>Habit training</td>
</tr>
<tr>
<td>HTBF</td>
<td>Habit training incorporating direct visual biofeedback</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>INVEST</td>
<td>Standard panel of radio-physiological tests of colonic and anorectal function</td>
</tr>
<tr>
<td>JRMO</td>
<td>Joint Research Management Office</td>
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<tr>
<td>LTF</td>
<td>Lost To Follow-up</td>
</tr>
<tr>
<td>MYMOP2</td>
<td>Measure Yourself Medical Outcome Profile</td>
</tr>
<tr>
<td>NHS REC</td>
<td>National Health Service Research Ethics Committee</td>
</tr>
<tr>
<td>NHS R&amp;D</td>
<td>National Health Service Research &amp; Development</td>
</tr>
<tr>
<td>PAC-QOL</td>
<td>Patient Assessment of Constipation Quality of Life questionnaire</td>
</tr>
<tr>
<td>PAC-SYM</td>
<td>Patient Assessment of Constipation Symptoms Questionnaire</td>
</tr>
<tr>
<td>Participant</td>
<td>An individual who takes part in a clinical trial</td>
</tr>
<tr>
<td>PCSG</td>
<td>Primary Care Society for Gastroenterology</td>
</tr>
<tr>
<td>PCTU</td>
<td>Pragmatic Clinical Trials Unit</td>
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<tr>
<td>PHQ-9</td>
<td>Patient Health Questionnaire -9</td>
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<td>PHQ-15</td>
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<td>PI</td>
<td>Principal Investigator</td>
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<td>PIS</td>
<td>Participant Information Sheet</td>
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<tr>
<td>PMG</td>
<td>Programme Management Group</td>
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<tr>
<td>PPIG</td>
<td>Patient and Public Involvement Group</td>
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<tr>
<td>PRO</td>
<td>Patient Reported Outcomes</td>
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<tr>
<td>PSC</td>
<td>Programme Steering Committee</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RAIR</td>
<td>Rectoanal inhibitory reflex</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SDV</td>
<td>Source Document Verification</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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<tr>
<td>WP</td>
<td>Work Package</td>
</tr>
</tbody>
</table>
2. SIGNATURE PAGE

**Chief Investigator Agreement**
The clinical study as detailed within this research protocol (*Version 1.0, dated 2Sep2014*), 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: 2Sep2014

**Principal Investigator Agreement** (if different from Chief investigator)
The clinical study as detailed within this research protocol (*Version 1.0, dated 2Sep2014*), 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: Carolynne Vaizey
Principal Investigator Site: St Marks Hospital at Northwest Hospitals NHS Trust
Signature and Date:
Signature and Date:

Principal Investigator Name: Dr Anton Emmanuel
Principal Investigator Site: University College Hospital London
Signature and Date:

Principal Investigator Name: Dr Andrew Williams
Principal Investigator Site: Guy’s and St Thomas’ NHS Foundation Trust
Signature and Date:

Principal Investigator Name: Dr Kathryn Gill
Principal Investigator Site: Sandwell and West Birmingham Hospital
Signature and Date:

Principal Investigator Name: Dr Yan Yiannakou
Principal Investigator Site: County Durham and Darlington NHS Foundation Trust
Signature and Date:
Principal Investigator Name: Dr Karen Nugent
Principal Investigator Site: University Southampton NHS Foundation Trust
Signature and Date:

Principal Investigator Name: Dr Ian Lindsay
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Signature and Date:

Principal Investigator Name: Dr Marc Mercer Jones
Principal Investigator Site: Queen Elizabeth Hospital Gateshead
Signature and Date:

Principal Investigator Name: Dr Chris Spearman
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Signature and Date:

Principal Investigator Name: Dr Karen Telford
Principal Investigator Site: University Hospital of South Manchester
Signature and Date:

Principal Investigator Name: Dr Mike Lamparelli
Principal Investigator Site: Dorset County Hospital
Signature and Date:

Principal Investigator Name: Dr Andrew Miller
Principal Investigator Site: University Leicester NHS Foundation Trust
Signature and Date:

Principal Investigator Name: Dr Steven Brown
Principal Investigator Site: Sheffield Teaching Hospital, NHS Foundation Trust
Signature and Date:
Statistician Agreement

The clinical study as detailed within this research protocol (Version 1.0, dated 2Sep2014), 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:
2Sep2014
### SUMMARY/SYNOPSIS

<table>
<thead>
<tr>
<th><strong>Short Title</strong></th>
<th>CapaCiTY study 1</th>
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<tbody>
<tr>
<td><strong>Methodology</strong></td>
<td>Randomised trial of habit training vs. habit training with biofeedback in adults with chronic constipation</td>
</tr>
<tr>
<td><strong>Research Sites</strong></td>
<td>NHS Trusts in England focussing on specialist pelvic floor centres; primary care networks in England;</td>
</tr>
<tr>
<td><strong>Objectives/Aims</strong></td>
<td>To determine:</td>
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<td></td>
<td>(1) whether a complex nurse-led intervention (pelvic floor retraining using biofeedback) is more effective than standardised nurse-led habit training</td>
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<td></td>
<td>(2) whether outcomes of such nurse-led interventions are improved by stratification to complex or standardised therapy based on prior knowledge of anorectal and colonic pathophysiology</td>
</tr>
<tr>
<td><strong>Number of Participants/Patients</strong></td>
<td>600 (227 HT, 227 HTB &amp; 146 INVEST)</td>
</tr>
<tr>
<td><strong>Main Inclusion Criteria</strong></td>
<td>Chronic constipation in adults (18-70 years) as defined by pragmatic clinical criteria [self-reported symptom duration &gt; 6 months; failure laxatives and lifestyle modifications]</td>
</tr>
<tr>
<td><strong>Statistical Methodology and Analysis (if applicable)</strong></td>
<td>Two hypotheses will be tested:</td>
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<tr>
<td></td>
<td>• Habit training with biofeedback (HTBF) results in a 15% increase in treatment response (from 42.5% to 57.5%) based on a reduction in PAC-QOL score of 1 point at 6 months compared to habit training (HT) alone in unselected adults with CC (50% combined response).</td>
</tr>
<tr>
<td></td>
<td>• Stratification to either HT or HTBF informed by pathophysiological investigation (INVEST) results in an overall 15% increase (i.e. to 65%) in treatment response based on a reduction in PAC-QOL score of 1 point at 6 months compared with NoINVEST randomised treatment.</td>
</tr>
<tr>
<td></td>
<td>A standardised outcome framework including clinical and health economic outcomes as well as qualitative data will be employed.</td>
</tr>
<tr>
<td><strong>Proposed Start Date</strong></td>
<td>03.11.14</td>
</tr>
<tr>
<td><strong>Proposed End Date</strong></td>
<td>31.03.18</td>
</tr>
<tr>
<td><strong>Study Duration</strong></td>
<td>41 months</td>
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3. INTRODUCTION

5.1 Background

Burden of disease
Constipation is common in adults and children and up to 20% of the population report this symptom depending on definitions used (2-28% adults; 0.7-30% children)\(^1\)\(^-\)\(^3\), with a higher prevalence in women\(^1\)\(^4\)\(^5\) and the elderly\(^6\). Chronic constipation (CC), usually defined as more than 6 months of symptoms, is less common\(^6\) 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 (probably about 1-2% population)\(^7\). Such patients, who are very frequently female\(^8\), 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\(^9\) and the effect of symptoms on measured QOL is significant\(^10\). CC consumes significant healthcare resources. In the US in 2012, a primary complaint of constipation was responsible for 3.2 million physician visits\(^11\) 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\(^12\) and the annual spend on laxatives exceeds £80m, with 17.4 million prescriptions in 2012 (Health and Social Care Information Centre, 2013)\(^13\).

Pathophysiological basis of chronic constipation
The act of defaecation 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\(^14\) 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. Patients with intractable symptoms and impaired QOL may subsequently be offered a range of costly, irreversible surgical interventions with unpredictable results\(^17\)\(^,\)\(^18\), 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\(^19\)\(^,\)\(^20\), and for adults with faecal incontinence\(^21\). 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\(^17\)\(^,\)\(^26\)\(^-\)\(^28\) it is timely that the currently limited evidence base 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 expenditures 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 I] and includes a series of interlinked studies that answer the important questions for patient care. A rolling program of national recruitment will provide a large cohort of well-defined patients for 3 subsequent studies over 5 years. The focus will be on generating real life evidence from pragmatic studies which will provide valid clinical outcome measures, and address 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.

5.2 Specific clinical background to the trial

In most UK practices, patients are first referred to specialist nurses for a variety of nurse-led behavioural interventions to improve defaecatory function. A range of cohort studies\textsuperscript{29}, RCTs\textsuperscript{30-35}, reviews\textsuperscript{36}, guidelines\textsuperscript{37}, meta-analysis\textsuperscript{38} and a Cochrane review\textsuperscript{39} attest to the general success of this approach. However opinion varies greatly concerning the complexity of intervention required and UK survey evidence indicates that there is remarkable variability of practice.

The most basic form of behavioural therapy comprises ‘habit training’ (HT). This involves optimising dietary patterns to maximise the gastro-colic response, which is associated with morning clustering of high amplitude propagated colonic contractions which propel contents towards the rectum for subsequent evacuation\textsuperscript{40}. Dietary advice to optimise intake of liquid and fibre is given as well as advice about frequency and length of toilet visits and posture. Patients are also instructed on basic gut anatomy and function, and gain an appreciation of how psychological and social stresses may influence gut functioning. Simple pelvic floor exercises are often included.

More complex forms of therapy include instrument-based biofeedback learning techniques\textsuperscript{29-35}. Favoured in the USA, and by about half of UK centres, these provide direct visual computer-based biofeedback of pelvic floor activity, usually displayed as real-time pressure or EMG activity during defaecation manoeuvres (e.g. ‘bearing down’) or attempted balloon expulsion. While small RCTs suggest an additive value of biofeedback over habit training alone in the management of selected patient subgroups of CC\textsuperscript{31 41-43}, there has been no multicentre or adequately powered RCT in unselected patients despite this uncertainty and significant resource implications. There is even controversy about which subgroups are benefited: some studies suggest only those with proven puborectalis incoordination\textsuperscript{41 42} whilst others are less exclusive\textsuperscript{29 31}. Further, most publications advocating biofeedback have come from specialist centres with considerable ‘investment’ in these techniques with much less favourable reports when biofeedback is the ‘de-vested’ comparator\textsuperscript{44 45}. These data (and their heterogeneity) have been coalesced in a recent Cochrane review by one of the study principle investigators (Norton)\textsuperscript{39}.

Despite being widely employed, there is conflicting evidence as to whether radiological and physiological investigations influence outcomes in CC with significant differences of expert opinion. Some advocate early complex and expensive investigations to guide treatment in most patients\textsuperscript{9} whereas others undertake such tests only in resistant cases or those progressing to surgery\textsuperscript{46}. The advantage of guiding treatment\textsuperscript{42 47} is balanced against the invasive nature of some tests, radiation exposure, embarrassment and cost (circa \£600-1200 NHS tariff): all currently require an escalation of care from primary care to hospital, and most currently necessitate an escalation of care from a secondary to tertiary centre. The need to resolve this question has been consistently highlighted\textsuperscript{37 48 49}; however, it can only really be addressed by evaluating long-term outcomes from treatment with or without these tests. Of particular relevance is the possibility that nurse-led therapies (as above) could be stratified using these tests. Notably, there is evidence that habit training with biofeedback (HTBF) may maximally benefit patients with certain pathophysiologicals\textsuperscript{35 41-43 50 51}, especially ‘functional defaecation disorder’ (FDD)\textsuperscript{37 52 53}. 

Version 1.0 15Sep2014 CapaCITY study 1
5.3 Rationale and Risks/Benefits

The overall rationale is to address 2 main objectives (see below). This is fulfilled by a parallel three arm, randomised trial design which permits two randomised comparisons: an overall evaluation of the performance of a panel of radio-physiological investigations (INVEST) in improving the selection of treatment and an evaluation of treatment options (HT vs. HTBF) without INVEST procedures. Thus the overall evaluation addresses whether INVEST-guided care leads to more favourable outcomes compared to randomised allocation. This study is possible because of the distribution of stratification factors in the INVEST arm based on international criteria for FDD52, which (fortuitously) are met by approximately 50% of adult patients with CC based on UK data (although the data monitoring plan allows for some statistical tolerance around this assumption).

The risks of participation are considered very low. The interventions proposed are those already offered to patients in specialist centres throughout the UK and internationally. The only difference conferred by participation is that these interventions will be randomly allocated and very carefully assessed. All interventions are safe. 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.

The benefits of participation are that patients will receive a very high standard of monitored care as a consequence of the detailed protocol. In some instances (geographically), patients may receive interventions for which they did not previously have access.

6. TRIAL OBJECTIVES

6.1 Primary objectives

(1) To determine whether a complex nurse-led intervention (pelvic floor retraining using biofeedback: HTBF) is more clinically effective than standardised nurse-led habit training (HT)

(2) To determine whether clinical outcomes of such nurse-led interventions are improved by stratification to complex or standardised therapy based on prior knowledge of anorectal and colonic pathophysiology using standardised radio-physiological investigations (INVEST)

6.2 Secondary objectives

(1) To determine relevant health economics for both interventions and for INVEST

(2) To qualitatively evaluate patient and health professional experience for interventions and INVEST

6.3 Endpoints

Clinical endpoints

All clinical endpoints will be coalesced into a single standardised outcome framework (this framework is constant throughout the other CapaCiTY programme studies).
Primary Clinical Endpoint

- Response to treatment defined as a 1-point (or greater) reduction in PAC-QOL score at 6 months post end of treatment.

Secondary Clinical Endpoints

To 24 months or end study

- PAC-QOL: binary responder analysis to treatment (as above) at (3, 6, 12, 18, 24 months post end of treatment);
- PAC-QOL: individual domains and total score (as continuous variables); at (3, 6, 12, 18, 24 months post end of treatment);
- PAC-SYM score: individual domains and total score (as continuous variables); at (3, 6, 12, 18, 24 months post end of treatment;
- A two week patient diary (for 2 weeks prior to each assessment) to record bowel frequency and whether each evacuation was ‘spontaneous (no use of laxatives) and / or complete’; journal will also capture concurrent medication, health contacts, time away from normal activities (including work) since the patient’s last visit; at (3, 6, 12, 18, 24 months post end of treatment;
- Generic QOL: 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, at 3, 6, 12, 18, 24 months post end of treatment.

To 12 months only

- Validated patient problem specific measure: Measure Yourself Medical Outcome Profile MYMOP2 (incorporates two worst volunteered symptoms and measure of wellbeing) at 3, 6 and 12 months post end of treatment.
- Patient Health Questionnaire-9 (PHQ-9 ) at 3, 6 and 12 months post end of treatment.
- Generalized anxiety disorder questionnaire (GAD7) at 3, 6 and 12 months post end of treatment.
- Global patient satisfaction / improvement score (VAS) and whether they would recommend each treatment experienced to other patients at 3, 6 and 12 months post end of treatment.
- 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-BROQ), and brief illness perception questionnaire BIPQ (CC)

Health economic outcomes

- Interventions, treatment sequelae and other health resource use related to the care of CC will be recorded in natural units and costed 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 and health professional experience

Face-to-face, digitally recorded, semi-structured interviews will be conducted involving a, diverse sample of patients and professionals at purposefully selected at various time points throughout the study (before starting to gauge expectations, during treatment to explore fidelity and ease of adherence, immediately after and up to 2 years after intervention to explore perspectives on the intervention and longevity of any benefit and pattern of response over time. 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. Approximately 50 interviews will be conducted with patients and 10 with professionals delivering the intervention, as follows:
• 10 INVEST and 10 No-INVEST participants to elucidate the experience of undergoing tests, being given an explanation of results, or feelings about not being tested;
• 15 HT and 15 HTBF patients, both improved and not improved (at 6 months) for perceptions of treatment
• 10 therapists involved in HT/HTBF to determine comparative ease of delivery of the 2 therapies;

Recruitment to interviews will continue until apparent data saturation. The interviews will be conducted by an experienced qualitative researcher. Professionals will be interviewed in clinic locations; patients will be interviewed in clinic locations or in their own home according to their preference. All patients will be told that they might be invited for interview when they are initially informed about the study. Participants will be contacted by the clinical team and if interested in being interviewed a separate PIS will be provided. Separate informed consent will be taken for interviews. Interviews will be digitally recorded and transcribed verbatim by a professional transcriber using a secure file transfer system.

Interviews will explore health, patients’ experiences of recruitment, individual interventions (INVEST and HT or HTBF treatments), their delivery, and patients’ views about outcome measures. Interviews will be conducted throughout to capture relatively early and later experiences and perceptions of the interventions. A topic guide for each of the interviews, informed by the existing literature and our patient advisors, will be developed.

7. METHODOLOGY

7.1 Inclusion Criteria

• Age 18-70 years
• Patient self-reports problematic constipation
• Symptom onset > 6 months prior to recruitment
• Symptoms meet American College of Gastroenterology definition of constipation
• Constipation failed treatment to a minimum basic standard (NHS Map of Medicine 2012\textsuperscript{65} (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

The study will use the American College of Gastroenterology definition\textsuperscript{64} of constipation (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).

7.2 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 prior 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 if known not an exclusion).
• Major colorectal resectional surgery
• Current overt pelvic organ prolapse (bladder, uterus, rectum) or disease requiring obvious surgical intervention
• Previous pelvic floor surgery to address defaecatory problems: posterior vaginal repair, STARR and rectopexy; previous sacral nerve stimulation
• Rectal impaction (as defined by digital and abdominal examination: these form part of the NHS Map of Medicine basic standard)\(^6\)\(^5\)
• Significant neurological disease deemed to be causative 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\(^6\)\(^5\) Barthel index <=11]
• Major active psychiatric diagnosis [schizophrenia, major depressive illness and mania]
• 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.
• Previous nurse-led bowel management
• Pregnancy or intention to become pregnant during study period.

7.3 Study Design / Plan – Study Visits

7.3.1 Setting
Specialist centres across England with a mix of urban and rural referral bases will be complemented by local primary care networks.

7.3.2 Recruitment
Patients attending medical services (primary through to specialist centres: outpatient clinics; GI physiology units) for constipation will be eligible for recruitment and assessed against the eligibility criteria. Identification of existing patients with CC in primary care will be aided by patient identification centres (PICS) associated with each trial site. Database searches may also aid patient identification in primary care e.g. the Clinical Effectiveness Group (CPCPH) has a dataset of 800,000 primary care records streamed in from practices in London in real time and collaboration with the Primary Care Society for Gastroenterology (PCSG) will identify other similar regional networks and databases. Database searches will be conducted by the primary care providers for the patients. Further PICS will be enrolled as required to meet recruitment schedule (see project management section 18).

7.3.3. Visit 0: Pre-Screening: Eligibility assessment
Patients referred from primary care or identified in secondary or tertiary care clinics will be approached by a suitably trained and delegated local researcher who will screen for basic eligibility by phone (or face-to-face interview based on patient choice) on the basis of a simplified inclusion / exclusion criteria proforma (i.e. self reported constipation for more than 6 months, difficulty passing stool, infrequent passing of stool, at least 2 medications tried for relief of symptoms). Patients will be recorded on a screening log and each will be allocated a sequential trial screening number. Patients will be provided with adequate explanation of the aims, methods, anticipated benefits and risks of the relevant interventions and will take away or be posted an invitation letter and patient information sheet. Patients will 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 will be allocated as follows:
Study Code S01
Site Code – 3 letter code for each site (APPENDIX III)
Participant Code – 4 digit code given consecutively and attributed at each site
For example, the first participant screened at Bart’s Health Trust would be assigned the code S01-BHT-0001. If they were then recruited to the study, they retain the same number with the S removed, upon consent, become, 01-BHT-0001 on the enrolment log. Participants progressing to other studies within the CapaCiTY programme will retain this number for pathway tracking.

7.3.4 Visit 1: Screening, consent and baseline assessments
Visit 1 will be conducted face to face in clinic (i.e. GI physiology). Following a detailed discussion about the trial, basically 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 performed within 3 months). Thereafter, additional baseline outcome assessments will be conducted. These include several key validated assessments that profile patients for important characteristics informing disease pathophysiology and important 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 coalesced into a single booklet (design and presentation have been optimised by patient representatives).

Screening/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/vagina

Baseline outcome assessments
- Baseline outcome assessments [PAC-QOL, PAC-SYM, MYMOP2, EQ-5D-5L & EQVAS, PHQ9, GAD7, CC-BRQ and BIPQ-CC,
- see endpoints above]
- Baseline 2-week patient diary and journal will be given

Other baseline only assessments
- Constipation(2006)\textsuperscript{67} and IBS(2006)\textsuperscript{68} modules of Rome III questionnaire
- Cleveland Clinic constipation questionnaire\textsuperscript{69}
- PHQ15
- Brief, chronic pain, autonomic\textsuperscript{70} and joint hypermobility\textsuperscript{71} assessments.
- St Marks Incontinence score (for concurrent symptoms)\textsuperscript{63}

Randomisation will be completed at the end of visit 1 (see section 8.3)

INVEST, radio-physiology and stratification will occur following randomisation and before the first intervention visit 2. (Section 8.5.3)

7.3.5 Visits 2-5: Interventions
Participants randomised to treatment without INVEST will undergo 4 sessions of standardised therapy (HT or HTBF) [detail below 8.5.1-8.5.2]. Those undergoing INVEST will have additional radio-physiological investigations [detail below 8.5.3] prior to being stratified to receive either HT or HTBF. Urinary pregnancy testing will be made available to women of child-bearing potential at eligibility assessment and advice will be given to all women regarding need to prevent pregnancy during the study intervention period. Serum pregnancy testing will be mandatory for women of childbearing potential randomized to the INVEST group based on the NHS 10 day rule (see interventions). All participants will be asked to complete the 2 week patient diary (see above) prior to INVEST, HT or HTBF interventions and prior to stopping laxatives. Thus the minimum delay for No-INVEST participants between visit 1 and visit 2 is 2 weeks. The INVEST participants must, in addition, wait a minimum of 2
further weeks for investigations to proceed as they are required to stop all laxatives prior to transit studies. The maximum wait time to first intervention regardless of randomisation will be 3 months.

7.3.6 Visit 6-10: Follow-up outcome assessments

A full standardised outcome framework, health economic and qualitative dataset will be recorded at baseline, 3, 6 and 12 months from end of treatment. The 6 month time-point at which the primary outcome is recorded will coincide with the end of a protocol-imposed ‘quarantine’ period during which participant’s response to therapy will remain un-confounded by treatment progression. In order to maximise completeness of data collected, the 3, 6 and 12 month follow up visits will be conducted face to face in clinic wherever possible. Follow up visits at 18 and 24 months can however be conducted by phone.

For participants not changing therapy (within or without the programme), further abbreviated outcomes only (PAC-SYM, PAC-QOL and EQ-5D-5L only) will be recorded at 18 and 24 months from the end of treatment (or the end of the programme if this is sooner).

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, after which the participant will be considered lost to follow up. (See criteria for withdrawal.)
### 7.3.7 Study Scheme Diagram

**CHRONIC CONSTIPATION** ~ 3000 pts in primary & secondary care
CC treatment to basic standard

- **Failure** ~ 1500 pts

**PRE-SCREENING & INFO GIVEN**
~ 1200 eligible referrals

**SCREENING & CONSENT**
~ 600 pts

- **Baseline assessments**
- **Randomised allocation**

**Visit 0**
- Minimum 24h

**Visit 1**
- Minimum 2 weeks

- **Intervention visits (2-6)**
  ~ 3 months duration

- **7% loss to follow up**

- **6 month follow up visit**

- **12-24 months**

- **Habit training**
  227 pts

- **Habit training & biofeedback**
  227 pts

- **Invest guided treatment**
  146 pts

- **Habit training**
  212 pts

- **Habit training & biofeedback**
  212 pts

- **Invest guided treatment**
  136 pts

**Primary and secondary outcome assessments**

**Follow up outcome assessments**
8. STUDY PROCEDURES

8.1 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.

8.2 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.

8.3 Randomisation Procedures
For the purpose of clarity, the study design has been presented as a 3 arm, parallel group RCT. Randomisation will be delivered at one point in time following recruitment (after eligibility and baseline assessments). Randomisation will be stratified by sex and centre.

The Pragmatic Clinical Trials Unit will develop an online randomisation system. Randomisation will be conducted by suitably trained and delegated researchers at recruiting sites and will follow the PCTU validated standard operating procedure for the study. An automatic email will notify the chief investigator, principal investigator, trial manager of randomisations performed. This will be a blinded notification.

8.4 Blinding
Patients and clinicians are necessarily aware of both INVEST and treatment allocations. However, all quantitative (but not qualitative) outcome assessments will therefore be analysed by investigators and statisticians who are blind to allocation status and index intervention. In addition, to minimize bias, where possible, a blinded researcher will collect outcome data.

8.5 Study interventions

8.5.1 Habit training (HT)
Habit training will be provided by trained specialist (nurse or physiotherapist with clinical experience) who has undertaken a standard one day training session (study specific). A standardised approach and intervention will be provided via use of an intervention manual; at least one random observation visit will be performed early in the study by lead research nurses for quality control.

The course of therapy will include 3-4 sessions (with interval tolerance of every 3-5 weeks). The first and last session will always be face to face. Sessions will be delivered by the same therapist if at all possible and tailored to participant’s individual needs. Each recruiting site will provide sufficient resource to cover visits in therapist absence or holiday.

Sessions (minimum 3; maximum 4): (45-60 mins).
This will use a standardised proforma. Participants will receive:
(a) A written information leaflet covering normal bowel function; causes of constipation; diet and fluid advice; getting into a good bowel habit.
(b) Review of written information using teaching tools;
(c) Advise to stop all laxatives including drugs that the BNF describes as having laxative effect or over the counter herbal teas that contain strong purgatives. Glycerine suppositories 1-2 as rescue if no stool for 3 days is allowed. No use of irrigation devices or enemas.
(d) Participants encouraged to follow a daily routine: sit on toilet 20-30 mins after first meal and / or hot drinks (sooner if urge felt);
(e) Participants can attempt defaecation after meals or when urge is felt no more than 3 times per day.
(f) Participants should sit on toilet with knees bent to 45 degree position with feet elevated on stool or equivalent; abdominal brace and breathe while performing anal relaxation.
(g) Participants must only attempt to push for 5-10 minutes maximum.
(h) Defaecation manoeuvres while the patient is positioned on chair with verbal coaching to breathe while pushing.
(i) Strongly discourage participants from multiple attempts and prolonged straining.
(j) No digitation anally.
(k) Where appropriate, the participant will be taught rectocele (vaginal), perineal and perianal splinting.
(l) Diet and lifestyle advice e.g. moderate but not excessive fibre; moderate but not excessive fluid intake; increase exercise e.g. walking if possible.
(m) Only participants with evacuation difficulty and / or perineal descent will be taught pelvic floor exercises.
(o) Plenty of optimism, encouragement and personal attention.
(p) Suggestions of what to work on until next meeting.
(q) Therapist to complete relevant sections in participant booklet

8.5.2 Habit training and direct visual biofeedback (HTBF)

Each session will incorporate all features of HT intervention (above) but also include direct visual biofeedback using the Sandhill Ultima (portable) system + HRaM catheter (Sandhill, Colorado, USA) connected to laptop biofeedback computer monitor. Calibration, validation and maintenance of the equipment will follow the built in Sandhill program and training manuals provided and recorded on the system at each session. Training on the system will be performed and documented in the investigator site file prior to sites commencing treatment.

a. At each session: biofeedback balloon and catheter/probe will be connected to biofeedback computer monitor. Patient lying in lateral position facing computer screen (supine if unable to lie in lateral position). Probe taped or held into position.
b. Resting pressure noted (event recorder). Squeeze pressure noted.
c. Rectal balloon inflated to assess first sensation and urge volume. Volumes noted. Maximum fill 200mL.
d. RAIR elicited with 60mL or volume to first urge air and effect on resting pressure noted.
e. Coaching to evacuate with 60mL air (one syringe full) in the balloon. Participant will attempt balloon expulsion whilst the effect on anal pressure is noted.
f. Monitor attempts to relax while pushing and expel balloon. Instruct participant to push and breathe emphasising need to push from the waist while relaxing anus. Note propulsive effort. A minimum of three 3 and no more than 10 attempts in total, with coaching (therapist observes abdominal and anal activity and advises), or until balloon is expelled (not essential). Correct pushing technique.
g. Sandhill HRaM can also be used to coach pelvic floor exercises if indicated.
h. Participants undergoing biofeedback may have rectal hypersensitivity or hyposensitivity. At each interventional visit, these participants will undergo sensitivity training. The goal will be to increase (hypersensitive) or decrease (hyposensitive) tolerated balloon volume by gentle progressive distension or depression of air.

The outcome of each session will note the ability to expel the balloon, generate propulsion, increase rectal pressure, relax the anal canal, and ability to sense the balloon at lower or higher volumes (relevant to hypo and hyper-sensate patients) over successive sessions will be recorded on intervention CRF. Pseudo-anonymised raw traces of the above events will be saved as files for further research interpretation and validation within the study.
Both interventions

Telephone support will be available from therapist between visits (number given, office hours only). The therapist will complete an intervention CRF at every visit or participant contact. In the instance of new psychological issues being determined during consultation, referral for psychological support will be deferred until after completion of behavioural interventions. The exception to this rule would be where there is clinical concern regarding the participants acute mental state requiring more urgent intervention (see withdrawal from treatment criteria).

8.5.3 INVEST- radio-physiology and stratification (guided treatment)

Radio-physiological investigations

Equipment will be standardised across participating sites. The Sandhill Ultima HRaM system will be used with a standard laptop. Calibration, validation and maintenance of the equipment will follow the built in Sandhill program and training manuals provided and recorded on the system at each session. Training on the system will be performed and documented in the investigator site file prior to sites commencing treatment.95

Participants allocated to INVEST will undergo standardised investigations (below) prior to stratification of therapy: Routine NHS practice (10 day NHS rule) will apply in respect of women between menarche and menopause. Participants randomised to this group who may potentially be pregnant will have a serum pregnancy test performed as per routine care.

(a) Anorectal manometry using high resolution methods92-94 to determine defined abnormalities of rectoanal pressure gradient (see below for definition of FDD) during simulated evacuation37,78,73;
(b) Balloon sensory testing using standardised methods74 75 (2ml water 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 adults76. The rectoanal inhibitory reflex will also be elicited by 50ml rapid inflation (if necessary 100ml);
(c) Fixed volume (50ml) water-filled rectal balloon expulsion test37 72 77 78 in the seated position on a commode. Abnormal expulsion is defined as abnormal if failure to expel with 1-minute effort79; for men and 1.5 minutes for women79;
(d) Whole gut transit study using serial (different shaped) radio-opaque markers over 3 days with single plain radiograph at 120 hours80 8681.
(e) Fluoroscopic evacuation proctography using rectal installation of barium porridge to defaecatory desire threshold (or maximum 300ml) and evacuation on a radiolucent commode82-86 with pre-opacification of the small bowel (for enterocele). Radiation dose, proportion of contrast evacuated and time taken will be recorded, as well as ‘functional’ (i.e. pelvic floor dyssynergia) and ‘structural’ features deemed obstructive to defaecation (e.g. rectocele, enterocele and intussusception)37 76 87.

Stratification for therapy

Participants will be given the results of investigations by the physiologist or radiologist. The assimilated results will then be sent to one of 3 designated investigators for analysis. A diagnosis of ‘functional defaecation disorder’ (FDD) will be made by assimilation of results from tests (b, c and e) by an agreed protocol based on well-established international ROME III criteria37 52. These results will be reviewed centrally by two observers independently (Taylor and Scott) using secure data sharing platform (2 week turnaround).

Rome III Criteria require 2 of the following 3 findings to diagnose FDD.
• Evidence of impaired evacuation, based on failed balloon expulsion test or proctography (failure to expel 65% contrast in 2½ minutes);
• Inappropriate contraction of pelvic floor or < 20% relaxation basal anal pressure on push manoeuvre (manometry) or proctographic evidence of failed puborectalis relaxation or paradoxical contraction;
• Inadequate propulsive forces assessed by manometry or proctography.

Treatment
Participants with FDD will undergo habit training and direct visual biofeedback (HTBF) as above (8.5.2). Those without FDD will undergo HT only (8.5.1). Within the HTBF allocated participants, those with rectal sensory dysfunction (hyper or hyposensation) will have balloon volumes directed to also addressing this abnormality (see interventions).

8.6 Concomitant Medications
It is inevitable that participants 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 diary for this purpose (within the patient diary (see standardised outcome framework). A concomitant medications list including a shortlist of contributory or confounding medications will be used to filter on data entry.

8.7 Criteria for Discontinuation
The interventions proposed are well-established in current clinical practice and have no safety concerns. There are no defined criteria for discontinuation. Additionally, if the DMEC committee, 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; safety concerns, proof of effectiveness or serious and persistence non-compliance/serious breaches. If the study is terminated participants will be returned to the NHS normal follow up and routine care.

8.8 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.

<table>
<thead>
<tr>
<th>Study Assessment</th>
<th>Data Sources</th>
<th>Data Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief screening and eligibility criteria check</td>
<td>Patient Interview</td>
<td>CRF1</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>Consent Form</td>
<td>none</td>
</tr>
<tr>
<td>Structered history including eligibility assessment, demographics, medical history, medications and joint hypermobility variable and clinical examination</td>
<td>Patient interview and Medical Notes - routine data</td>
<td>CRF2</td>
</tr>
<tr>
<td>Pregnancy Test where applicable</td>
<td>Laboratory Test Result - routine data</td>
<td>CRF2</td>
</tr>
<tr>
<td>(Rome III ConstipationQ &amp; IBSQ, Cleveland ClinicQ, PHQ15)</td>
<td>PRO – Baseline Questionnaire</td>
<td>Baseline Questionnaire</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Randomisation</td>
<td>Online system</td>
<td>none</td>
</tr>
<tr>
<td>Rectal balloon sensory testing</td>
<td>Medical Notes - routine data</td>
<td>CRF3</td>
</tr>
<tr>
<td>Balloon expulsion test</td>
<td>Medical Notes - routine data</td>
<td>CRF3</td>
</tr>
<tr>
<td>Anal manometry</td>
<td>Medical Notes - routine data</td>
<td>CRF3</td>
</tr>
<tr>
<td>Radio-opaque marker transit study</td>
<td>Medical Notes - routine data</td>
<td>CRF3</td>
</tr>
<tr>
<td>Evacuating proctogram</td>
<td>Medical Notes - routine data</td>
<td>CRF3</td>
</tr>
<tr>
<td>In therapy assessments (HT, HTBF).</td>
<td>Medical Notes - routine data</td>
<td>CRF4</td>
</tr>
<tr>
<td>Standardised Outcome Assessments - (PAC-QOL, PAC-SYM, MYMOP2, EQ-5D-5L, EQVAS, PHQ9, GAD7, VAS, CC-BRQ, BIPQ-CC)</td>
<td>PRO – Outcome Questionnaires</td>
<td>Outcome Questionnaire</td>
</tr>
<tr>
<td>Short outcome assessment (PAC-QOL, PAC-SYM, EQ-5D-5L)</td>
<td>PRO – Short Outcome Questionnaire</td>
<td>Short Outcome Questionnaire</td>
</tr>
<tr>
<td>Patient Diary &amp; Journal</td>
<td>PRO – Patient Diary and Journal</td>
<td>Patient Diary and Journal</td>
</tr>
<tr>
<td>AE log</td>
<td>Medical Record and PRO</td>
<td>CRF5</td>
</tr>
<tr>
<td>ConMed Log</td>
<td>Medical Record and PRO</td>
<td>CRF6</td>
</tr>
<tr>
<td>Deviation Log</td>
<td>CRF7</td>
<td>CRF7</td>
</tr>
<tr>
<td>Note to File/Contact Log</td>
<td>CRF8</td>
<td>CRF8</td>
</tr>
<tr>
<td>Early Withdrawal</td>
<td>Medical Record</td>
<td>CRF9</td>
</tr>
<tr>
<td>Study Completion</td>
<td>Medical Record</td>
<td>CRF10</td>
</tr>
<tr>
<td>Follow Up</td>
<td>PRO – Diary and Journal</td>
<td>CRF11</td>
</tr>
</tbody>
</table>

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 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).

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 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.

**8.9 Follow-up Procedures**
The study duration allows for follow up to a maximum of 24 months with data collection at 3, 6, 12, 18 and 24 months post end of therapy. Thereafter, participants will leave the study and return to ‘routine clinical care’ as determined within their local NHS institution (or be recruited to subsequent trials).

8.10 Laboratory Assessments

Serum Pregnancy Testing will be performed as per standard care for any women of childbearing potential randomised to the INVEST group only.

8.11 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). Fluoroscopy is required for evacuation proctography, with a maximum screening time of 3 minutes. These procedures form 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.

8.12 Procedure for un-blinding if applicable

Patients and therapists are not blinded to the intervention. There is no foreseeable need for the study statistician to be un-blinded during the course of the study.

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

Individual participants will be able to drop out at any time of either the treatment or the study. Data will be retained for intent to treat analysis from all participants after the point of consent and recruitment unless the participant specifically withdraws consent for their data to be used.

Withdrawal from treatment criteria (no further interventions but follow up data collected):

Participants will be withdrawn from the study interventions if they develop any of the following exclusion criteria;

- Becomes pregnant or intends to become pregnant (only in baseline and intervention phases)
- Subsequently diagnosed with proven cause for secondary constipation e.g. Parkinson’s disease or bowel obstruction
- Requires new medication with proven effects on bowel function e.g. opioids
- Develops significant intercurrent illness precluding participation
- Requires surgery or other intervention (other than minor ops) during treatment or follow up phase
- Develops acute psychological problem causing safety concern

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

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 choses to withdraw and does not wish to participate in follow up data collection
- Death or significant incapacity making follow up data collection impossible

8.14 Schedule of Assessment
<table>
<thead>
<tr>
<th>Assessment</th>
<th>V0 Pre-Screening by visit or telephone</th>
<th>V1 Screening and Baseline</th>
<th>V2* Intervention assessments</th>
<th>V3-V5 Intervention assessments</th>
<th>V6-V7 3&amp;6 month follow up visit</th>
<th>V8 12 month Follow up visit</th>
<th>V9-10 18 &amp;24 month Follow up assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Timeframe from baseline (Maximum Timeframe)</td>
<td>-1 day</td>
<td>0</td>
<td>+2 weeks (HT/HTBF) +4 to 12 weeks (INVEST)</td>
<td>+4 weeks (+/-) 1week</td>
<td>+3 months</td>
<td>+ 6 months</td>
<td>+6 months</td>
</tr>
<tr>
<td>Brief screening and providing PIS</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>Informed Consent</td>
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<td>Structured history including eligibility assessment, demographics, medical history, medications, clinical examinations and pain and joint hypermobility variables.</td>
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<td>Pregnancy Test where applicable</td>
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<td>Baseline assessments (Rome IIIQ – ConstipationQ &amp; IBSQ, Cleveland Clinic Q, PHQ15,)</td>
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<td>Rectal balloon sensory testing*</td>
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<td>Balloon expulsion test*</td>
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<td>Evacuating proctogram*</td>
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<td>In therapy assessments (HT, HTBF).</td>
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<td>Standardised outcome framework assessments (PAC-QOL, PAC-SYM, MYMOP2, EQ-SD-5L, EQVAS, PHQ9, GAD7, CC-BRQ, BIPQ-CC, VAS)</td>
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<td>Short Outcome Assessment (PAC-SYM, PAC-QOL, EQ-SD-5L)</td>
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<td>Patient Diary and Journal provided</td>
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<td>Patient Diary and Journal Collected</td>
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<td>Adverse Event and Concomitant Medication Review</td>
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*Allow up to minimum 4 weeks and maximum 3 months for INVEST only radio-physiology assessments between randomisation and first intervention. Maximum duration of participation for invest group – 31 months. Maximum duration of participation for HT&HTBF groups – 28 months.
8.15 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.

8.16 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, success or failure of the primary outcome, 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.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size
The sample size has been calculated using the primary clinical outcome: proportion of patients achieving a 1 point reduction in PAC-QOL score\textsuperscript{54}. This widely used, psychometrically robust measure of overall treatment response with concurrent validity to patient global ratings of success has been used by previous trials of behavioural therapies in CC\textsuperscript{55}.

For a chronic condition such as CC, a difference of 15% in the primary outcome can be considered clinically important\textsuperscript{22} and also the notional minimum required to justify the cost and invasive nature of INVEST, or of a more complex and expensive treatment (HTBF over HT alone).

In the HT vs. HTBF randomised arm, we hypothesize, based on previous literature that for unselected patients (No INVEST), the overall outcome will be approximately 50%. To detect a change of 15% around this mean (from 42.5% to 57.5%) with the addition of biofeedback to HT requires 212 patients per arm at 85% power and a significance level of 0.05.

To detect an increase in proportion of patients with a successful outcome from a mean of 50% in the No-INVEST arms to 65% in the INVEST arm at a significance level of 5% with a power of 85% requires 136 patients. Previous research from trials\textsuperscript{30,34,35,41,42} and reviews\textsuperscript{37-39} indicates that the outcome of HTBF in patients with INVEST-defined FDD is about 80% (range 70-88%) regardless of exact regimen used, and thus that we might reasonably expect an overall response rate of 65% (based on 50% patients having INVEST-defined FDD: calculation = (80+50)/2).

Allowing for a 7% loss to follow up, a sample size of 227 is needed in the HT and HTBF arms and 146 in the INVEST arm. A total sample size of 600 patient’s across the three arms. The sample size and dropout rate assumptions will be revisited by the DMEC in an interim sample size calculation and the ratio of recruitment adjusted
if necessary. If a larger dropout rate occurs, it will be possible to recruit further patients over and above that suggested in each arm to maintain study power.

9.2 Method of Analysis

9.2.1 Clinical outcomes

The primary outcome will be analysed on intent-to-treat at the 6-month time-point (prior to progressing to further condition-specific care). The proportion of participants achieving a 1 point reduction in PAC-QOL score will be analysed using logistic regression with a random effect for centre and fixed effects for intervention, gender, baseline PAC-QOL and breakthrough medication.

Secondary outcomes will be analysed at 6-months and at additional time-points (3, 12, 18 and 24 months from end of treatment). Outcomes will take the form of count (change in number of symptom episodes), ordinal (patient’s global impression of success) and continuous (questionnaire scores) data. Regression models, with a random effect for centre, appropriate to the outcome data types will be fitted to estimate the treatment effect, adjusting for baseline values (when appropriate), gender, and breakthrough medication use as a potential confounder.

Predictive modelling using 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. Appropriate regression models will be developed to determine the influence of these pre-treatment characteristics on the success of treatments in all work packages.

Analysis will be performed using proprietary software (Stata, Stata Corp. Texas) by the appointed study statistician. P<0.05 will be taken to indicate statistical significance. No analyses will be conducted until a statistical analysis plan (SAP) has been written and reviewed by an independent statistician. The SAP will be approved by the senior statistician and chief investigator. Multiple imputation will be used to address missing values. Subgroup analyses will be performed for selected baseline characteristics.

9.2.2 Health economic outcomes

Within-trial stochastic analysis will compare the cost/success and cost/QALY of INVEST and biofeedback. Patient-level cost-effectiveness analysis will use standard bootstrapping methods to generate cost-effectiveness acceptability curves exploring value-for-money.

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 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. For example, it will be possible to ask whether INVEST or No-INVEST-led first line care leads to lower overall costs or improved outcomes. 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% for costs and benefits).

### 9.2.3 Qualitative interviews

Interviews will be digitally recorded, anonymised, transcribed verbatim and analysed using a pragmatic thematic analysis and NVivo8 software (QSR International Ltd, Warrington, UK) for data management. Data analysis will be developed as outlined by Fereday & Muir-Cochrane in the first instance by mapping key concepts derived from the transcripts ('charting') and extracting emergent themes from the transcripts. Prof Norton and Lesley Dibley will conduct independent analyses and then compare and refine resulting codes and themes in discussion. Emergent themes, together with captured observational data, will form the basis of analytical interpretation.

### 10. ETHICS

#### 10.1 General

The study 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 3 studies will however have separate protocols and patient information sheets to 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 separate information sheets consent forms for each individual study within one pragmatic enriched programme design with Dr Art Tucker, previously the national ethics advisor and Chair of the East London and the City REC who confirms this will be practicable.
10.2 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 the standardised outcome framework, outcomes will be first undertaken at a fixed interval of 3 months from the end of each intervention. For a period of 6 months, patients will not progress to further therapies thus preventing outcome ‘contamination’. This ‘quarantine’ period from major therapy progression is required to give a reasonable clinical impression of outcome. This delay is akin to that in usual NHS care during which general supportive care will be provided while further interventions are considered. Thus, this proposed ‘quarantine’ period to 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 1 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 1 will be consented as a distinct single entity.

The investigating team have no conflicts of interest.

11. SAFETY CONSIDERATIONS:

There are no safety considerations attributable to the interventions. Patients allocated to INVEST-guided therapy will undergo two radiological procedures (whole gut transit study and evacuation proctography) using ionising radiation as outlined above. The combined dose of these procedures (~1.2 mSv) is equivalent to less than 7 months 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.

12. DATA HANDLING AND RECORD KEEPING:

12.1 Confidentiality

Information related to participants will 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. All case report forms will be pseudonymised. The participant’s GP will be informed of their participation in the study, but they may opt out at the time of consent.

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.

12.2 Record Retention and Archiving

When the research trial is complete, it is a requirement of the Research Governance Framework and BH Trust Policy that the records 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.

13. LABORATORIES (if applicable)

Serum pregnancy testing will be performed by local NHS pathology laboratories

14. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

14.1 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 practice (although the manufacturer of the balloon catheter system for HTBF will be unified for standardisation across the study sites). 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 and during direct visual biofeedback.
2. Direct visual biofeedback equipment. Sandhill Ultima (portable) system + Unisensor HRaM catheter (300 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. HRaM catheters and rectal balloons for anal manometry / rectal sensory testing: various suppliers (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 including radiolucent commode for proctogram (part of INVEST- see above).

14.2 Techniques and interventions
There are no experimental techniques within the study. The interventions (HT and HTBF are outlined in detail above).

14.3 Data Collection Tools
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.

- Measure Yourself Medical Outcome Profile MYMOP2 (Registered user with Univ. Bristol);
- 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.

The permissions / licenses to use the below instruments has 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: use from MAPI Research Trust
- EQ-5D-5L:

14.4 Medicinal product
None

15. SAFETY REPORTING

15.1 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 intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

As this is a non-CTIMP trial, no medicinal products are being administered as part of the trial. All trial interventions are as per the standard care provided within the NHS for chronic constipation. Therefore, unrelated adverse events will not be recorded on the CRF. Causality will be at the discretion of the health care provider (e.g. research nurse, physiotherapist, principal investigator or delegated member of team). 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. 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.

15.2 Serious Adverse Event (SAE)
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 Sponsor and REC where in the opinion of the Principal 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.

15.3 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 CI and sponsor within 24 hours of the site learning of the event and by the coordinating team to the REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to NRES website and JRMO SOPs.

15.4 Expected SAE’s
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.

15.5 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 where possible discuss an USM with the sponsor prior to implementation and then to inform the sponsor (in writing) and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) SOP for amendments should be followed For further guidance on this matter, please refer to NRES website and JRMO SOPs.

15.6 Annual Safety Reporting
The CI will send the Annual Progress Report to the REC using the NRES template (the anniversary date is the date on the REC “favourable opinion” letter from the REC) and to the sponsor. Please see HRA website and JRMO SOP for further information.

15.7 Overview of the Safety Reporting Responsibilities
The CI has the overall pharmacovigilance and safety oversight responsibility. The CI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor’s requirements.

*Communication organogram for reporting SAE’s*

SAE recorded on AE log

L PI assesses SAE and reports to CI within **24 hours**, PI reports to local institution as per local protocol

L CI reports related and unexpected SAE’s to PCTU QA manager and Sponsor within **24 hours of PI becoming aware of event**

L CI reports related and unexpected SAE’s to REC within **15 days**

CI reports to DMEC every **6-12 months**

CI reports **annually** to REC

SAEs will be followed up until resolution.
16. 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 discussed and 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 were 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.

17. 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 the study is conducted in accordance with the principles of Good Clinical Practice (GCP) and 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,
- assist in resolving problems brought to it by the Programme Management Group (PMG),
• monitor the progress of the trial and adherence to protocol and milestones
• consider new information of relevance from other sources,
• consider and act on the recommendations of the data monitoring and ethics committee (DMEC), sponsor and/or REC,
• review trial 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 and study 3 lead (Knowles)
• Study 1 lead PIs (Emmanuel & Norton)
• Senior statistician (Eldridge)
• Health Economist (Mason)
• Study 2 lead (Yan Yiannakou)
• An independent chair (Professor John McLaughlin, Professor of Gastroenterology and Nutrition, University of Manchester)
• Programme Manager (Stevens)
• External independent members (Prof David Jayne, Professor of Surgery, University of Leeds) including PPI (Mr Ian McCurrach, Deborah Gilbert and Louise Smalley).

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 1 lead PIs (Emmanuel & Norton)
• 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 two weeks prior to the PSC to enable recommendations to be fed forward. The DMEC will comprise:
• An independent lead (Dr Daniel Altman, UCL)
• A further appointed independent statistician
• One other independent health scientist.
A DMEC 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.

Patient and Public Involvement Group (PPIG) will be managed by the PMG and Bowel and Cancer Research Charity. The PPIG may be involved in:

- Review of participant information sheets, booklets, diaries and advertising/marketing materials
- Project management by representation on the PSC
- Dissemination of results and lay summaries
- Presentations at local research events
- Patient focus groups and workshops

18. PROJECT MANAGEMENT

18.1 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 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 the effectiveness of data collection tools and participant information 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 SAEs and serious breaches within required timelines.
- 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.

18.2 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.
18.3 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 IV. Projected recruitment rates are:

- 01.11.14  first participant
- 31.01.15  60 participants
- 30.04.15  120 participants
- 31.07.15  180 participants
- 31.10.15  240 participants
- 31.01.16  300 participants
- 30.04.16  360 participants
- 31.07.16  420 participants
- 31.10.16  480 participants
- 31.01.17  520 participants
- 30.04.17  last (600th) participant
Estimated milestones are:

- **Milestone I:** 01.11.14: 1st participant recruited
- **Milestone II:** 01.12.14: 1st participant intervention
- **Milestone III:** 01.02.15: 1st participant completes intervention
- **Milestone IV:** 31.01.16: 300 (half) participants recruited
- **Milestone V:** 30.04.17: last participant recruited
- **Milestone VI:** 31.07.17: last participant finished intervention
- **Milestone VII:** 31.04.18: last primary endpoint recorded at 6 month follow up

15. **FINANCE AND FUNDING**

The study is being financed by an NIHR PGfAR award: RP-PG-0612-20001: £1,991,653. Additional resource will be provided via host CLRNs. The calculation of all costs and contracting has been performed in conjunction with the sponsor.

16. **INDEMNITY**

Queen Mary University London has agreed to act as study sponsor. Insurance and indemnity will be provided by the sponsor.

17. **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. Authorship at the head of the primary results paper will be cited as a collaborative group to avoid giving undue prominence to any individual. 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.

18. **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 individual participants, users and carers who have been involved in, or otherwise contributed to, the programme;

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 co-applicant (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 Bart’s NIHR HTC for GI disease. Results will be disseminated by the HTC newsletter / website to all 90 UK industrial and all 25 clinical colorectal centres.

7. **A 2 day international meeting entitled ‘Current perspectives in chronic constipation’** will be hosted at QMUL. This meeting will be planned again for 2019 to coincide with the outputs of the programme.
19. REFERENCES

14. Poulton B TS. The Nursing Cost of


34. Chiarioni G, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology 2006;130(3):657-64.


55. Dubois D, Gilet H, Viala-Danten M, Tack J. Psychometric performance and clinical meaningfulness of the Patient Assessment of Constipation-Quality of Life questionnaire in prucalopride (RESOLOR) trials for


95. Sandhill Scientific Training

http://cs1.starcast.net/index.htd?a-globals-global_id=182
20. APPENDICIES

APPENDIX I – CapaCiTY programme
APPENDIX II – NHS Map of Medicines

Constipation - suspected

http://healthguides.mapmedicine.com/schemes/map/constipation_in_adult_and_the_elderly.html

- Information
  - Regional
  - Local Info
  - Notes

- Primary care
  - Secondary care

- Constipation - clinical presentation
  - History and examination
  - Consider organic causes of constipation
    - Organic cause suspected
      - Refer to specialist advice and treatment
    - Refer to appropriate services
    - On to secondary care - suspected

- Intestinal bowel syndrome (IBS) suspected
  - On to IBS suspected
  - Initial treatment of bowel complaint
    - Consider further treatment
      - Chronic constipation
        - Treatment of acute constipation
        - Treatment in pregnancy or breastfeeding women
      - Dehydration
        - Dehydration management
      - Dehydration - management

- Idiopathic cause suspected
  - Idiopathic cause suspected

- Diabetes cause suspected
  - Diabetes cause suspected

- Obstetric cause suspected
  - Obstetric cause suspected

- General cause suspected
  - General cause suspected

- Comorbidity cause suspected
  - Comorbidity cause suspected

- Other causes of constipation suspected
  - Other causes of constipation suspected

- Decision:
  - Initial treatment of bowel complaint
    - Consider further treatment
      - Chronic constipation
        - Treatment of acute constipation
        - Treatment in pregnancy or breastfeeding women
      - Dehydration
        - Dehydration management
      - Dehydration - management

- Initial treatment of bowel complaint
  - Initial treatment of bowel complaint

- Other causes of constipation suspected
  - Other causes of constipation suspected
### APPENDIX III – Site Codes

<table>
<thead>
<tr>
<th>NHS Trust</th>
<th>Site Code</th>
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<tr>
<td>Bart’s Health NHS Trust [Knowles]</td>
<td>BLT</td>
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<tr>
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<td>SMH</td>
</tr>
<tr>
<td>University College Hospital London [Emmanuel]</td>
<td>UCL</td>
</tr>
<tr>
<td>Guy’s and Thomas’ NHS Foundation Trust London [Williams]</td>
<td>GST</td>
</tr>
<tr>
<td>Sandwell and West Birmingham NHS Trust [Gill]</td>
<td>SWB</td>
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<td>Oxford University Hospitals NHS Trust [Lindsay]</td>
<td>OUH</td>
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<td>Queen Elizabeth Hospital Gateshead [Mercer-Jones]</td>
<td>QEH</td>
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<td>Norfolk and Norwich University Hospitals NHS Foundation Trust [Spearman]</td>
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<td>Sheffield Teaching Hospital NHS Foundation Trust [Brown]</td>
<td>STH</td>
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### APPENDIX IV – Study Gantt chart

**CapaCITY Trial 1**  
**CHRONIC CONSTIPATION TREATMENT PATHWAY**

<table>
<thead>
<tr>
<th>Year</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<tbody>
<tr>
<td>Month</td>
<td>March</td>
<td>May</td>
<td>July</td>
<td>Sep</td>
<td>Nov</td>
<td>Jan</td>
</tr>
</tbody>
</table>

#### Pre-study
- Staff Recruitment

#### Protocol Development
- Case Report Form Design
- Database Development
- PIS/CF design
- Randomisation System Set Up
- Trial SOPs
- EC Approval
- Site Feasibility Testing/Recruitment
- Site Submission and R&D approvals
- Site initiation and Training

#### Programme roll-out
- Convene PSC/DMC

#### Milestones / reports
- Milestones (see text)
- Data analysis
- Reports
- Convene PSC
- TMG

#### Funding
- Research only
- Research + NHS
- IP strategy

**CHRONIC CONSTIPATION TREATMENT PATHWAY**

<table>
<thead>
<tr>
<th>Year</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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</tr>
</tbody>
</table>

#### Recruitment study 1

#### Interventions study 1

#### Assessments study 1

#### Final

#### Convene PSC

#### DMC

#### TMG

#### Milestones (see text)

#### Data analysis

#### Reports

#### Convene PSC

#### TMG