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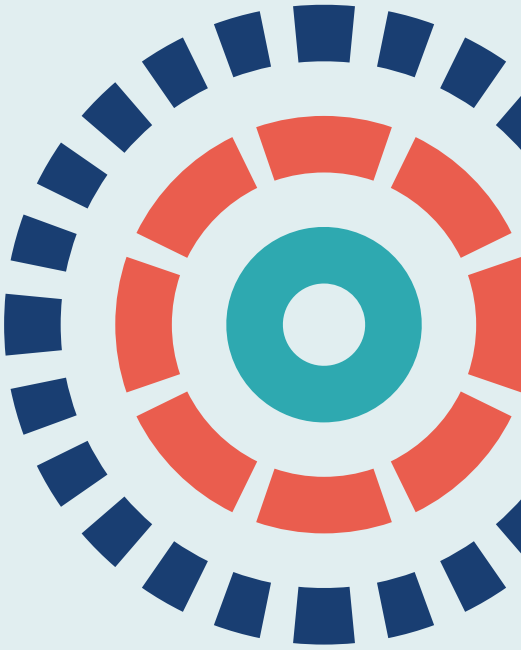

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Charles H Knowles,[1*] Lesley Booth,[2] Steve R Brown,[3,4] Samantha Cross,[5] Sandra Eldridge,[5] Christopher Emmett,[6] Ugo Grossi,[1] Mary Jordan,[7] Jon Lacy-Colson,[8] James Mason,[7] John McLaughlin,[9] Rona Moss-Morris,[10] Christine Norton,[11] S Mark Scott,[1] Natasha Stevens,[1] Shiva Taheri[1] and Yan Yiannakou[6]

[1]Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[2]Bowel Research UK, London, UK
[3]Sheffield Teaching Hospitals NHS Trust, Sheffield, UK
[4]School of Health and Related Research, University of Sheffield, Sheffield, UK
[5]Pragmatic Clinical Trials Unit, Institute of Population Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[6]Northumbria Healthcare NHS Foundation Trust, Newcastle upon Tyne, UK
[7]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
[8]Royal Shrewsbury Hospital, Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, UK
[9]Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[10]Department of Psychology, King's College London, London, UK
[11]Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, UK

*Corresponding author

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programme (but on an unrelated research area) and received consulting fees from EnteroMed Ltd (London, UK) and Coloplast A/S (Humlebæk, Denmark). He has received payment or honoraria from Medtronic plc and support for attending meetings/travel from Medtronic plc. He is chairperson of the European Society of Coloproctology Research Committee and the Bowel Research UK (London, UK) Grants Committee. Jon Lacy-Colson was a paid consultant to Origin Sciences Ltd (Cambridge, UK) during the course of the programme (but on an unrelated research area). Rona Moss-Morris reports ad hoc payments for workshop therapist training in cognitive–behavioural therapy for irritable bowel syndrome (a related syndrome), consultancy payments and stock options from Mahana Therapeutics, Inc. (San Francisco, CA, USA), and being a beneficiary of a licence agreement between King's College London (London, UK) and Mahana Therapeutics, Inc., for a digital version of cognitive–behavioural therapy for irritable bowel syndrome. S Mark Scott received honoraria from Laborie (Orangeburg, NY, USA) for teaching during the course of (but unrelated to) the programme. Yan Yiannakou has received a grant from McGregor Healthcare Ltd (Macmerry, UK) to research the burden of disease in constipation and use of irrigation. Christine Norton is chief investigator on another programme grant on symptom management in inflammatory bowel disease.

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Abstract

Non-drug therapies for the management of chronic constipation in adults: the CapaCiTY research programme including three RCTs

Charles H Knowles,[1*] Lesley Booth,[2] Steve R Brown,[3,4] Samantha Cross,[5] Sandra Eldridge,[5] Christopher Emmett,[6] Ugo Grossi,[1] Mary Jordan,[7] Jon Lacy-Colson,[8] James Mason,[7] John McLaughlin,[9] Rona Moss-Morris,[10] Christine Norton,[11] S Mark Scott,[1] Natasha Stevens,[1] Shiva Taheri[1] and Yan Yiannakou[6]

[1]Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[2]Bowel Research UK, London, UK
[3]Sheffield Teaching Hospitals NHS Trust, Sheffield, UK
[4]School of Health and Related Research, University of Sheffield, Sheffield, UK
[5]Pragmatic Clinical Trials Unit, Institute of Population Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[6]Northumbria Healthcare NHS Foundation Trust, Newcastle upon Tyne, UK
[7]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
[8]Royal Shrewsbury Hospital, Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, UK
[9]Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[10]Department of Psychology, King's College London, London, UK
[11]Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, UK

*Corresponding author c.h.knowles@qmul.ac.uk

Background: Chronic constipation affects 1–2% of adults and significantly affects quality of life. Beyond the use of laxatives and other basic measures, there is uncertainty about management, including the value of specialist investigations, equipment-intensive therapies using biofeedback, transanal irrigation and surgery.

Objectives: (1) To determine whether or not standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback is more clinically effective than standardised specialist-led habit training alone, and whether or not outcomes of such specialist-led interventions are improved by stratification to habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback or habit training alone based on prior knowledge of anorectal and colonic pathophysiology using standardised radiophysiological investigations; (2) to compare the impact of transanal irrigation initiated with low-volume and high-volume systems on patient disease-specific quality of life; and (3) to determine the clinical efficacy of laparoscopic ventral mesh rectopexy compared with controls at short-term follow-up.

Design: The Chronic Constipation Treatment Pathway (CapaCiTY) research programme was a programme of national recruitment with a standardised methodological framework (i.e. eligibility, baseline phenotyping and standardised outcomes) for three randomised trials: a parallel three-group trial, permitting two randomised comparisons (CapaCiTY trial 1), a parallel two-group trial (CapaCiTY trial 2) and a stepped-wedge (individual-level) three-group trial (CapaCiTY trial 3).

Setting: Specialist hospital centres across England, with a mix of urban and rural referral bases.

Participants: The main inclusion criteria were as follows: age 18–70 years, participant self-reported problematic constipation, symptom onset > 6 months before recruitment, symptoms meeting the American College of Gastroenterology's constipation definition and constipation that failed treatment to a minimum basic standard. The main exclusion criteria were secondary constipation and previous experience of study interventions.

Interventions: CapaCiTY trial 1: group 1 – standardised specialist-led habit training alone ($n = 68$); group 2 – standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback ($n = 68$); and group 3 – standardised radiophysiological investigations-guided treatment ($n = 46$) (allocation ratio 3 : 3 : 2, respectively). CapaCiTY trial 2: transanal irrigation initiated with low-volume (group 1, $n = 30$) or high-volume (group 2, $n = 35$) systems (allocation ratio 1 : 1). CapaCiTY trial 3: laparoscopic ventral mesh rectopexy performed immediately ($n = 9$) and after 12 weeks' ($n = 10$) and after 24 weeks' ($n = 9$) waiting time (allocation ratio 1 : 1 : 1, respectively).

Main outcome measures: The main outcome measures were standardised outcomes for all three trials. The primary clinical outcome was mean change in Patient Assessment of Constipation Quality of Life score at the 6-month, 3-month or 24-week follow-up. The secondary clinical outcomes were a range of validated disease-specific and psychological scoring instrument scores. For cost-effectiveness, quality-adjusted life-year estimates were determined from individual participant-level cost data and EuroQol-5 Dimensions, five-level version, data. Participant experience was investigated through interviews and qualitative analysis.

Results: A total of 275 participants were recruited. Baseline phenotyping demonstrated high levels of symptom burden and psychological morbidity. CapaCiTY trial 1: all interventions (standardised specialist-led habit training alone, standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback and standardised radiophysiological investigations-guided habit training alone or habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback) led to similar reductions in the Patient Assessment of Constipation Quality of Life score (approximately –0.8 points), with no statistically significant difference between habit training alone and habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback (–0.03 points, 95% confidence interval –0.33 to 0.27 points; $p = 0.8445$) or between standardised radiophysiological investigations and no standardised radiophysiological investigations (0.22 points, 95% confidence interval –0.11 to 0.55 points; $p = 0.1871$). Secondary outcomes reflected similar levels of benefit for all interventions. There was no evidence of greater cost-effectiveness of habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback or stratification by standardised radiophysiological investigations compared with habit training alone (with the probability that habit training alone is cost-effective at a willingness-to-pay threshold of £30,000 per quality-adjusted life-year gain; $p = 0.83$). Participants reported mixed experiences and similar satisfaction in all groups in the qualitative interviews. CapaCiTY trial 2: at 3 months, there was a modest reduction in the Patient Assessment of Constipation Quality of Life score, from a mean of 2.4 to 2.2 points (i.e. a reduction of 0.2 points), in the low-volume transanal irrigation group compared with a larger mean reduction of 0.6 points in the high-volume transanal irrigation group (difference –0.37 points, 95% confidence interval –0.89 to 0.15 points). The majority of participants preferred high-volume transanal irrigation, with substantial crossover to high-volume transanal irrigation during follow-up. Compared with low-volume transanal irrigation, high-volume transanal irrigation had similar costs (median difference –£8, 95% confidence interval –£240 to £221) and resulted in significantly higher quality of life (0.093 quality-adjusted life-years, 95% confidence interval 0.016 to 0.175 quality-adjusted life-years). CapaCiTY trial 3: laparoscopic ventral mesh rectopexy resulted in a substantial short-term mean reduction in the Patient Assessment of Constipation Quality of Life score (–1.09 points, 95% confidence interval –1.76 to –0.41 points) and beneficial changes in all other outcomes; however, significant increases in cost (£5012, 95% confidence interval £4446 to £5322) resulted in only modest increases in quality of life (0.043 quality-adjusted life-years, 95% confidence interval –0.005 to 0.093 quality-adjusted life-years), with an incremental cost-effectiveness ratio of £115,512 per quality-adjusted life-year.

Conclusions: Excluding poor recruitment and underpowering of clinical effectiveness analyses, several themes emerge: (1) all interventions studied have beneficial effects on symptoms and disease-specific quality of life in the short term; (2) a simpler, cheaper approach to nurse-led behavioural interventions appears to be at least as clinically effective as and more cost-effective than more complex and invasive approaches (including prior investigation); (3) high-volume transanal irrigation is preferred by participants and has better clinical effectiveness than low-volume transanal irrigation systems; and (4) laparoscopic ventral mesh rectopexy in highly selected participants confers a very significant short-term reduction in symptoms, with low levels of harm but little effect on general quality of life.

Limitations: All three trials significantly under-recruited [CapaCiTY trial 1, $n = 182$ (target 394); CapaCiTY trial 2, $n = 65$ (target 300); and CapaCiTY trial 3, $n = 28$ (target 114)]. The numbers analysed were further limited by loss before primary outcome.

Trial registration: Current Controlled Trials ISRCTN11791740, ISRCTN11093872 and ISRCTN11747152.

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List of abbreviations

A&E	accident and emergency department
AE	adverse event
AUC	area under the curve
BIPQ-CC	Brief Illness Perception Questionnaire for Chronic Constipation
CapaCiTY	Chronic Constipation Treatment Pathway
CC	chronic constipation
CC-BRQ	Chronic Constipation Behavioural Response to Illness Questionnaire
CCG	Clinical Commissioning Group
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRAG	Constipation Research Advisory Group
CRF	case report form
CRN	Clinical Research Network
DMEC	Data Monitoring and Ethics Committee
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EQ-VAS	EuroQol Visual Analogue Scale
ETC	excess treatment cost
EVPI	expected value of perfect information
FMI	fraction of missing information
FOCB	first observation carried back
GAD-7	Generalised Anxiety Disorder-7
GP	general practitioner
HRAM	high-resolution anorectal manometry
HT	standardised specialist-led habit training alone
HTBF	standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback
ICER	incremental cost-effectiveness ratio
ID	identifier
INVEST	standardised radiophysiological investigations
IQR	interquartile range
IRAS	Integrated Research Application System
ITT	intention to treat
lapVMR	laparoscopic ventral mesh rectopexy
LOCF	last observation carried forward
MAR	missing at random
MDD	major depressive disorder
MDT	multidisciplinary team
MyMOP2	Measure Yourself Medical Outcome Profile 2
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	net monetary benefit
PAC-QoL	Patient Assessment of Constipation Quality of Life
PAC-SYM	Patient Assessment of Constipation Symptoms
PCA	Prescription Cost Analysis
PCTU	Pragmatic Clinical Trials Unit
PHQ-9	Patient Health Questionnaire-9 items

PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12
PPI	patient and public involvement
PSC	Programme Steering Committee
QALY	quality-adjusted life-year
QoL	quality of life
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SAP	statistical analysis plan
STARR	stapled rectal resection
T	time (weeks) since randomisation
TAI	transanal irrigation
TwiCs	trials within cohorts
WP	work programme
WTP	willingness to pay

Plain English summary

Constipation affects nearly everyone at some stage in their life. However, about 1 in 100 people in the UK suffer chronic symptoms that fail to respond to simple treatments including exercise, drinking more fluid, better diet and laxatives.

We call this 'chronic constipation', and it can be very difficult to treat, even by experts. We can give stronger laxatives and newer drugs and provide nurse-led bowel retraining classes, bowel irrigation and even surgery. However, we do not know what tests we should do first and what treatments we should then use. The Chronic Constipation Treatment Pathway (CapaCiTY) programme enrolled 275 participants to three trials:

CapaCiTY trial 1 – how good are different types of specialist nurse-led bowel retraining (182 participants)?
CapaCiTY trial 2 – what type of bowel irrigation via the anus should we use (65 participants)?
CapaCiTY trial 3 – how good is a type of surgical operation called laparoscopic ventral mesh rectopexy for internal bowel prolapse (28 participants)?

Unfortunately, the studies did not recruit enough participants to tell us for sure which test or treatment is best; however, we were able to draw some useful conclusions by combining symptom and quality-of-life outcomes, costs of treatment and participant interview responses about their experience:

- All new treatments studied helped most participants.
- Simple nurse-led retraining programmes were at least as good as more costly, complex ones.
- Expensive tests did not help at an early stage.
- Participants prefer using higher-volume bowel irrigation than lower-volume bowel irrigation and it has better results.
- Despite worries about mesh, laparoscopic ventral mesh rectopexy seems safe in the short term and leads to a big drop in symptoms early after surgery. This was in very carefully chosen participants.
- The programme helped to ensure that we all use the same tests and nurse-led therapies. We also published the most detailed reviews so far, to our knowledge, of different types of surgery for chronic constipation.

Scientific summary

Background

Constipation is common in adults and children, with up to 20% of the population reporting this symptom depending on the definition used. Some people (1–2% of the population) suffer symptoms that are chronic, disabling and refractory to basic treatments. Such people, who are most commonly female, are usually referred to secondary care, with many progressing to tertiary specialist investigations. Patient dissatisfaction and health-care and societal costs are high in this group.

Management of chronic constipation (CC) is generally stepwise, with first-line conservative treatment, such as lifestyle advice and laxatives (primary care), followed by nurse-led bowel retraining programmes, sometimes including focused biofeedback (secondary/tertiary care). Such treatments are poorly standardised in the UK and far from universally successful. Patients with intractable symptoms and impaired quality of life (QoL) may subsequently be offered irreversible surgical interventions that have unpredictable results.

Objectives

The main aims of the Chronic Constipation Treatment Pathway (CapaCiTY) research programme were to trial the effectiveness of three current and popular interventions for CC.

CapaCiTY trial 1:

- to determine whether or not standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback (HTBF) is more clinically effective than standardised specialist-led habit training alone (HT) at 6 months' follow-up
- to determine whether or not outcomes of such specialist-led interventions are improved by stratification to HTBF or HT based on prior knowledge of anorectal and colonic pathophysiology using standardised radiophysiological investigations (INVEST).

CapaCiTY trial 2:

- to compare the impact of transanal irrigation (TAI) initiated with a low-volume and a high-volume system on patient disease-specific QoL after 3 months of treatment.

CapaCiTY trial 3:

- to determine the clinical efficacy of laparoscopic ventral mesh rectopexy (lapVMR) compared with controls at short-term follow-up (24 weeks).

In addition, the programme sought to:

- detail the baseline phenotype of UK patients with CC to identify symptom burden and psychological morbidity
- systematically review the outcomes of all current surgical interventions for CC
- synthesise results of all three trials with current evidence to produce a prototype treatment pathway for health-care decision-makers.

Methods and results

Standardised methodological framework, recruitment and baseline phenotyping

Participants met stringent eligibility criteria. The main inclusion criteria were age 18–70 years, symptom onset > 6 months prior to recruitment, symptoms meeting the American College of Gastroenterology's constipation definition and constipation that failed treatment to a minimum basic standard. The main exclusions were secondary constipation and previous experience of study interventions.

A total of 275 participants were recruited across three trials, representing a major shortfall in the required sample sizes ($n = 808$). This reflected several major process challenges but also low uptake from the 733 patients screened (37.1%). About half of screen failures were because participants failed eligibility and half were because participants declined. There were also problems of participant retention, with higher-than-anticipated loss before primary outcome (actual loss 11–43% vs. anticipated loss 20%).

Trial participants were 90% female (100% in CapaCiTY trial 3) and were a mean age of 45 years [interquartile range (IQR) 33–57 years]. Baseline phenotyping indicated high levels of comorbid medical disorders (> 70%) and a history of previous abdominal and pelvic surgery (> 50%). Risk factors such as psychiatric diagnoses and joint hypermobility were present in ≈ 20% of participants. Around two-thirds of women were parous. Although the criteria for chronicity of constipation was 6 months' duration, mean duration was 6 years and almost all participants with CC had constipation that proved intractable to lifestyle modification and laxatives, which was reflected by referral pattern (80% of referrals were from secondary or tertiary care). Almost 20% of these cases of CC were also refractory to prokinetic drug therapy. Levels of symptom burden were high, with mean Patient Assessment of Constipation Quality Of Life (PAC-QoL) and Patient Assessment of Constipation Symptoms (PAC-SYM) scores of > 2.0 points at baseline. In addition, > 50% of participants had faecal incontinence symptoms, > 30% had urinary symptoms and > 20% (100% in CapaCiTY trial 3) had pelvic organ prolapse symptoms. Levels of psychological morbidity were high. Cut-off points on the self-reported Patient Health Questionnaire-9 items (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) scale suggest that around one-third of participants would have met criteria for a depressive or anxiety disorder. These rates are six times higher than those reported in the general population and are on the higher end of mental comorbidity in patients with medical conditions.

Baseline data formed the basis of a subsequent standardised (for all three trials) panel of outcomes, including several validated symptom-scoring instruments, cost-effectiveness variables [i.e. individual-level patient costs from diaries and EuroQol-5 Dimensions, five-level version (EQ-5D-5L), scores to calculate quality-adjusted life-years (QALYs)] and qualitative methodology to determine participant experience (through a total of 45 interviews). The primary clinical outcome was mean change in validated PAC-QoL score. Secondary clinical outcomes included a range of validated disease-specific (PAC-SYM), generic [Measure Yourself Medical Outcome Profile 2 (MyMOP2)] and psychological [GAD-7, PHQ-9, Brief Illness Perception Questionnaire for Chronic Constipation (BIPQ-CC)] scoring instrument values.

CapaCiTY trial 1: habit training with direct visual biofeedback compared with habit training alone in adults with chronic constipation

We sought to answer the question of whether or not, in unselected participants with CC, a more time-consuming, expensive and invasive procedure (namely, instrument-directed visual biofeedback) added benefit to that achieved by a more basic programme of nurse-led bowel education – namely, habit training. We compared HT with HTBF. In addition, because of strongly held views (mainly in the USA) that biofeedback works only for a subset of patients with CC who have dyssynergic defaecation (a specific functional disorder), we used a battery of UK-standardised specialist tests of anorectal and colonic function (INVEST) to stratify participants to one treatment or the other. Both treatments were provided by trained NHS specialist colorectal nurses or physiotherapists.

To answer both research questions concurrently required a sample size of 394 participants (based on 3 : 3 : 2 randomisation to HT, HTBF and INVEST treatment, respectively). Unfortunately, the CapaCiTY trial 1 recruited only 182 participants, and only 103 participants provided primary outcome data at 6 months after cessation of therapy. With the caveat that all results were underpowered, there was no evidence that HTBF conferred additional benefit over HT {HT: PAC-QoL score at baseline, 2.26 points [standard deviation (SD) 0.69 points], vs. at 6 months post treatment, 1.49 points [SD 0.85 points]; HTBF: PAC-QoL score at baseline, 2.41 points [SD 0.81 points] vs. at 6 months post treatment, 1.65 points [SD 1.03 points]; treatment difference −0.03 points, 95% confidence interval (CI) −0.33 to 0.27 points; $p = 0.8445$}. Secondary outcomes also reflected equal beneficial effects of both HT and HTBF on a range of symptom and QoL outcomes (e.g. mean PAC-SYM scores decreased from 2.2 points at baseline to 1.5 points at 6 months and weekly laxative use decreased fourfold). Global satisfaction was 65%, reflecting participants who liked or disliked both interventions for a number of reasons. Similar results were obtained for INVEST vs. no INVEST, with no difference in primary outcome [INVEST: mean PAC-QoL score at baseline, 2.33 points (SD 0.74 points) vs. at 6 months post treatment, 1.56 points (0.93 points); no INVEST: mean PAC-QoL score at baseline 2.36 points (0.78 points) vs. at 6 months post treatment, 1.81 points (1.03 points); treatment difference 0.22 points, 95% CI −0.11 to 0.55 points; $p = 0.1871$]. Participants provided reasons for liking INVEST, for example greater knowledge of their condition (and knowing that their condition was not 'all in their mind'), and described disliking the invasiveness of, and embarrassment caused by, the tests. Given similar changes in EuroQol-5 Dimensions, five-level version (EQ-5D-5L), scores for all interventions, cost-effectiveness analyses favoured the simpler (i.e. HT and no INVEST) strategies as the dominant strategies. For both HTBF and INVEST, cost increases were significant (HTBF vs. HT: £239, 95% CI £133 to £354; INVEST vs. no INVEST: £543, 95% CI £403 to £685) and QoL was actually reduced compared with HT (HTBF: −0.010 QALYs, 95% CI −0.053 to 0.03 QALYs; INVEST: −0.047 QALYs, 95% CI −0.093 to −0.001 QALYs). The probability that HT is cost-effective was a *p*-value of 0.83 at a willingness-to-pay (WTP) threshold of £30,000 per QALY.

CapaCiTY trial 2: pragmatic randomised controlled trial of low-volume compared with high-volume initiated transanal irrigation therapy in adults with chronic constipation

A total of 65 participants were randomised (low-volume TAI, $n = 30$; high-volume TAI, $n = 35$) from a target sample size of 300 participants. At 3 months, there was a modest reduction in PAC-QoL scores in the low-volume TAI group, from a mean of 2.4 points to a mean of 2.2 points (SD −0.2 points); there was a greater reduction in mean score in the high-volume TAI group, of 0.6 points (difference −0.37 points, 95% CI −0.89 to −0.15). Substantially greater crossover from low-volume to high-volume TAI over the follow-up period ($n = 18$) than from high-volume to low-volume TAI ($n = 6$) indicated a preference for high-volume TAI. Compared with low-volume TAI, high-volume TAI had similar costs (−£8, 95% CI −£240 to £221) but was associated with significantly greater QoL (0.093 QALYs, 95% CI 0.016 to 0.175 QALYs). Qualitative analysis reflected the view that the increased clinical effectiveness of high-volume TAI outweighed concerns about the slightly increased duration and discomfort.

CapaCiTY trial 3: stepped-wedge randomised controlled trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation

Seven high-quality systematic reviews of CC surgery with graded practice recommendations based on European consensus were published in 2017 confirming lapVMR as an evidential need. A total of 28 participants were randomised from a target sample size of 114 participants, and lapVMR resulted in substantial short-term reduction in PAC-QoL scores (−1.09 points, 95% CI −1.76 to −0.41 points) and beneficial changes in all other outcomes that were maintained to 72 weeks. There were few adverse events. However, significant increases in cost (£5012, 95% CI £4446 to £5322) resulted in only modest increases in QoL (0.043 QALYs, 95% CI −0.005 to 0.093 QALYs), with an incremental cost-effectiveness ratio of £115,512 per QALY at 48 weeks. Participant experiences were mixed, including participants who were globally satisfied, participants experiencing partial or transient benefits and participants who felt that it was not the 'miracle' cure they were looking for.

Conclusions

Firm conclusions are limited by significant under-recruitment. However, synthesis of clinical effectiveness and cost-effectiveness data with qualitative experience provides themes and suggestions for a CC pathway of care:

- In unselected CC patients, HT helps the majority, and the more costly, time-consuming and invasive intervention of HTBF should be reserved for special situations (specific diagnoses or perhaps failure of HT).
- Expensive and invasive radiophysiological investigations cannot be recommended early in the care pathway.
- The default for TAI should be high volume, with low volume reserved for special cases or patient preference.
- Care needs to be exercised in recommending surgery because, although surgery reduces constipation symptoms greatly in the short term, there was no evidence that surgery improved general QoL beyond 1 year.
- Future interventions should focus on incorporating psychological methods alongside HT to address psychological comorbidity.

Future research

It is not recommended that others try to repeat the CapaCiTY trials in their current form. First, it is unlikely that the main conclusions would vary despite further recruitment; second, lessons learned in respect of recruitment should deter others from trying to deliver parallel-group randomised controlled trials in this population, even with less explanatory designs. Future research could focus on better understanding the profound psychological comorbidity in the CC population and, if new interventions are to be trialled (including those co-addressing psychological and behavioural problems), these might be best suited to a design that incorporates experimental evaluations in a longitudinal cohort of participants, for example trials within cohorts studies. Such trials should seek to maximise pragmatism by sacrificing standardisation of specialist investigations and interventions in favour of uptake and recruitment; they would also benefit from an expanded network of centres (including outside the UK) to ensure timely recruitment and a greatly simplified and flexible follow-up regimen that could exploit advances in technology for remote follow-up.

Trial registration

These trials are registered as ISRCTN11791740, ISRCTN11093872 and ISRCTN11747152.

Funding

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SYNOPSIS

Background

Burden of disease

Constipation is common in adults and children, and up to 20% of the population (2–28% of adults and 0.7–30.0% children) report this symptom depending on the definition used,[1–3] with a much higher prevalence in women.[4–6] Chronic constipation (CC), usually defined as > 6 months of symptoms, is less common[7] but results in 0.5 million UK general practitioner (GP) consultations per annum. A proportion (1–2%)[8] of the population suffer more disabling symptoms, are very frequently female[9] and are usually referred to secondary care, with many progressing to tertiary specialist investigation. Patient dissatisfaction levels are high in this group, with ≈ 80% feeling that laxative therapy is unsatisfactory;[10] furthermore, the effect of symptoms on quality of life (QoL) is significant.[11] CC consumes significant health-care resources. In the USA in 2004, a primary complaint of constipation was responsible for 8 million physician visits,[12] resulting in (direct and indirect) costs of US$1.7B. Although detailed figures are lacking in the UK, it is estimated that ≈ 10% of district nursing time is spent on constipation[13] and that the annual spend on laxatives exceeds £100M.[14]

Pathophysiological basis of chronic constipation

The act of defaecation is dependent on the co-ordinated functions of the colon, rectum and anus. Considering the complexity of neuromuscular (sensory and motor) functions required to achieve planned, conscious and effective defaecation,[15] it is no surprise that disturbances to perceived 'normal' function occur commonly at all stages of life. Clinically, such problems commonly lead to de facto symptoms of obstructed defaecation (e.g. straining; incomplete, unsuccessful or painful evacuation; bowel infrequency), but symptoms such as abdominal pain and bloating are also very common. After exclusion of a multitude of secondary causes (e.g. 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, patients may be divided into those who have slow colonic transit, evacuation disorder, both or neither (e.g. no abnormality found with current tests). Evacuation disorders can be subdivided into those in which a structurally significant pelvic floor abnormality is evident, such as rectocele or internal prolapse (e.g. intussusception), and those in which there is a dynamic failure of evacuation without structural abnormality, most commonly termed functional defaecation disorder.

Management of chronic constipation

Management of CC is a major problem because of its high prevalence and lack of widespread specialist expertise. In general, a step-wise approach is undertaken, with first-line conservative treatment such as lifestyle advice and laxatives (primary care) followed by nurse-led bowel retraining programmes, sometimes including focused biofeedback and psychosocial support (secondary/tertiary care). Although these treatments may improve symptoms in more than half of patients, they are far from universally successful. Thus, patients with intractable symptoms and impaired QoL may be offered a range of costly, irreversible surgical interventions with unpredictable results, sometimes resulting in major adverse events (AEs) or a permanent stoma.

The research programme

An evidence-based pathway for the management of CC in adults is currently lacking, although National Institute for Health and Care Excellence (NICE) guidance exists for the management of CC in children[16–18] and for allied conditions (e.g. faecal incontinence) in adults. This arguably leads to variations in practice,

particularly in specialist services. With a number of new drugs gaining NHS approval[19–22] and new technologies at a horizon-scanning stage,[23–26] 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 health-care expenditures by appropriately sequencing the care provided while targeting more expensive therapies at those most likely to benefit from them. Such data could inform the development and commissioning of integrated care pathways.[27]

The overall rationale of the Chronic Constipation Treatment Pathway (CapaCiTY) research programme, therefore, was to develop an evidence base for CC management through a series of three randomised controlled trials (RCTs) that answered some of the important questions for sequenced patient care (*Figure 1*). For each, the focus was on generating real-life evidence based on valid clinical outcome measures, patient acceptability and cost.

The specific objectives were as follows:

- work programme (WP)1
  - to develop a common methodological framework for subsequent studies
  - to recruit a UK cohort of adults with CC based on strict eligibility criteria and detail the baseline phenotype to identify disease risk factors, symptom burden, QoL and psychological morbidity.
- WP2 (CapaCiTY trial 1)
  - to determine whether or not standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback (HTBF) is more clinically effective than standardised specialist-led habit training alone (HT)
  - to determine whether or not outcomes of such specialist-led interventions are improved by stratification to HTBF or HT based on prior knowledge of anorectal and colonic pathophysiology using standardised radiophysiological investigations (INVEST).
- WP3 (CapaCiTY trial 2)
  - to compare the impact of transanal irrigation (TAI) initiated with a low-volume and a high-volume system on patient disease-specific QoL after 3 months of treatment.
- WP4 (CapaCiTY trial 3)
  - to systematically review the evidence for all common surgical procedures used for adults with CC
  - to determine the clinical efficacy of laparoscopic ventral mesh rectopexy (lapVMR) compared with controls at short-term follow-up (24 weeks).
- WP5
  - to synthesise clinical outcome, patient acceptability and cost data from CapaCiTY trials and to develop an NHS pathway for the management of CC in adults based on data synthesis.

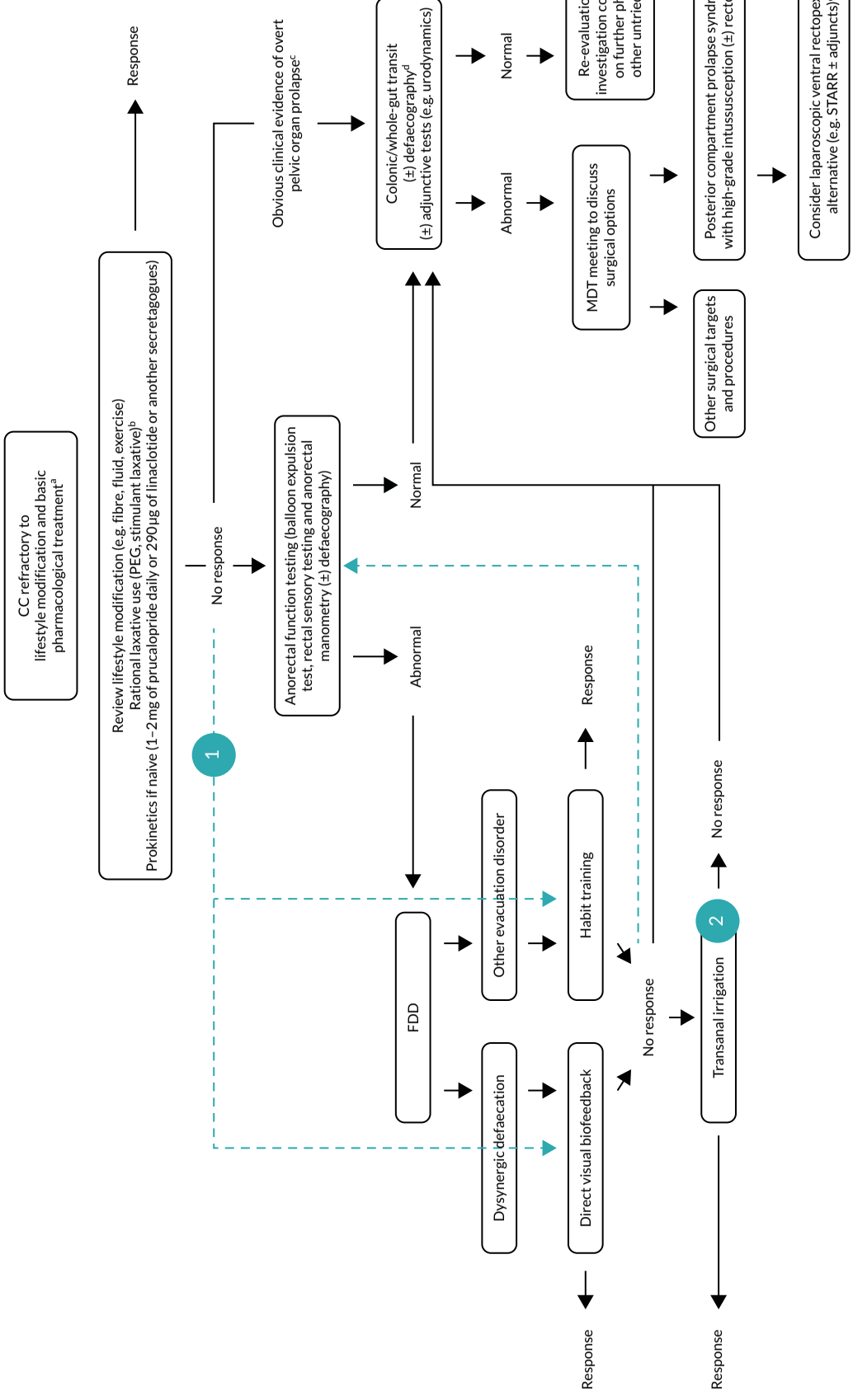

FIGURE 1 Overview of the CapaCITY research programme. Green arrows indicate studied pathways in CapaCITY trials 1–3 (numbered circles). a, Alarm features excluded and secondary causes treated appropriately; b, in IBS-C, consider antispasmodics or neuromodulators in case constipation improves but abdominal pain persists and is dominant symptom; c, examples of overt prolapse include anterior (stage 3 cystocele), middle (stage 3 rectocele, uterovaginal) and posterior compartments (grade IV/V intussusception); d, if not performed previously; e, common adjuncts include sacrocolpopexy, hysterectomy, transvaginal tape and cystocele repair. FFD, functional defaecation disorder; IBS-C, constipation-predominant irritable bowel syndrome; MDT, multidisciplinary team; PEG, polyethylene glycol[0]; STARR, stapled rectal resection.

Work programme 1: common methodological framework and participant recruitment

Common methodological framework

To permit the synthesis of all data at the end of the programme, we defined eligibility criteria, outcome measures and analytic methods that were common across all three trials. In addition, at the outset it was envisaged that some participants could move sequentially through more than one trial if a prior treatment had failed (although in practice this happened very infrequently because of delays in recruitment to all studies).

Setting

Following scoping during the programme development phase, we pre-identified 10 UK specialist centres that geographically encompass the north and south of England with a mix of urban and rural referral bases. Other centres were recruited for specific studies, especially in CapaCiTY trial 3.

Target population

The programme addressed the NHS management of CC in secondary and tertiary care, rather than the broader patient population with relatively short-lived or mild symptoms, receiving self-care or primary care management. This focus was pragmatic, given the concentration of expertise, diagnostics and biofeedback equipment in hospital settings. Based on well-established epidemiological data[28,29] (see *SYNOPSIS*, *Background*), the main target population was women of mean age 50 years.

Ethics approvals

The three trials had the following registration details and approvals:

- CapaCiTY trial 1
    - Research Ethics Committee (REC) reference 14/LO/1786
    - Integrated Research Application System (IRAS) 160709
    - ISRCTN11791740
    - date of REC approval: 6 December 2014.
- CapaCiTY trial 2
    - REC reference 15/LO/0732
    - IRAS 172401
    - ISRCTN11093872
    - date of REC approval: 6 July 2015.
- CapaCiTY trial 3
    - REC reference 15/LO/0609
    - IRAS 171006
    - ISRCTN11747152
    - date of REC approval: 6 July 2015.

Eligibility assessments

Patients were recruited at the time of clinical consultation at physician- and nurse-led clinics, and also at the time of investigation in gastrointestinal physiology units. All patients expressing initial interest were referred to the local lead investigator to screen case notes for eligibility.

Good clinical practice-trained local investigators determined eligibility by interview on the basis of defined inclusion/exclusion criteria. Participants were recorded on a screening log and each allocated a unique participant identifier (ID) number. Eligible subjects were then provided with an adequate explanation of the aims, methods, anticipated benefits and risks of the programme, and a participant information sheet. Special emphasis was placed on the long-term nature of the programme, time commitments and number of assessments required. Patients were telephoned 1 week later (or given an appointment) to allow appropriate time for them to consider their participation.

Inclusion and exclusion criteria

Inclusion criteria

Chronic constipation was defined according to pragmatic criteria, broadly, those employed for recent pivotal trials of prokinetics[19,22] and US guidance:[30]

- age 18–70 years
- patient self-reported problematic constipation
- symptom onset > 6 months prior to recruitment
- symptoms meeting American College of Gastroenterology definition of constipation ('unsatisfactory defaecation characterized by infrequent stool, difficult stool passage or both for at least previous 3 months')[30]
- constipation that has failed treatment to a minimum basic standard according to the NHS Map of Medicine[31] (lifestyle and dietary measures and two or more laxatives or prokinetics tried)
- ability to understand written and spoken English (for questionnaire validity).

Exclusion criteria

Exclusions included major causes of secondary constipation and specific factors precluding participation in study interventions:

- significant organic colonic disease (red flag symptoms e.g. rectal bleeding previously investigated); inflammatory bowel disease; megacolon or megarectum (if diagnosed beforehand); or severe diverticulosis, bowel stricture or birth defects deemed to contribute to symptoms (incidental diverticulosis not an exclusion criterion)
- major colorectal resection surgery
- current overt pelvic organ prolapse (e.g. bladder, uterus, rectum) or disease requiring obvious surgical intervention
- previous pelvic floor surgery to address defaecatory problems [posterior vaginal repair, stapled rectal resection (STARR) and rectopexy] or previous sacral nerve stimulation
- rectal impaction (as defined by digital and abdominal examination, which form part of the NHS Map of Medicine basic standard)[31]
- significant neurological disease deemed to be causative of constipation (e.g. Parkinson's disease), spinal injury, multiple sclerosis or diabetic neuropathy (uncomplicated diabetes alone not an exclusion criterion)
- significant connective tissue disease – scleroderma, systemic sclerosis and systemic lupus erythematosus (hypermobility alone not an exclusion criterion)
- significant medical comorbidities and activity of daily living impairment (based on a Barthel index[32] score of > 11 in apparently frail patients)
- major active psychiatric diagnosis (e.g. 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, and all regular strong opioid use
- pregnancy or intention to become pregnant during study period
- previous experience of specific therapies included in the programme.

Trial-specific inclusion criteria

- CapaCiTY trial 1:
  - vision sufficient to undertake visual biofeedback.
- CapaCiTY trial 2:
  - sufficient manual dexterity of patient/carer to use TAI.
- CapaCiTY trial 3:
  - failure of non-surgical interventions (minimum of nurse-led behavioural therapy)
  - internal rectal prolapse, as determined by clinical examination and INVEST, fulfilling two diagnostic criteria – (1) intra-anal or intrarectal intussusception with or without other dynamic pelvic floor abnormalities (e.g. rectocele, enterocele, perineal descent) and (2) deemed (by expert review) to be obstructing on defaecating proctogram (i.e. trapping contrast and/or associated with protracted or incomplete contrast evacuation using normal ranges).[33]

Baseline clinical evaluation

In addition to screening questions, clinical examination and information obtained by baseline standardised outcome assessments, participants completed a structured interview to document other comorbidities and risk factors (e.g. metabolic, endocrine and neurological disease; obstetric and gynaecological history; joint hypermobility; past surgical history). Clinical examination of the perineum/anus/rectum/vagina was carried forward to baseline from the last clinical consultation to prevent unnecessary repetition of intimate examinations.

Specialist radiophysiological investigations

All three trials required, at least in part (depending on the trial), the results of a number of well-established specialist investigations of anorectal and colonic functions. These investigations were nationally standardised during National Institute for Health Research (NIHR) programme development work, including a consensus meeting (London 2013) highlighting universally discordant current practice; remarkably, no UK centre at that time had the same protocol for any of the four main tests:[34]

1. Anorectal manometry using high-resolution methods[35–37] to determine defined abnormalities of rectoanal pressure gradient during simulated evacuation.[38–40]
2. Balloon sensory testing using standardised methods[41,42] (2 ml of air per second to a maximum of 360 ml) to determine volume inflated to first constant sensation, defaecatory desire and maximum tolerated volumes. Rectal hyposensation and hypersensation defined in accordance with sex-specific normative data on 91 healthy adults.[43] The rectoanal inhibitory reflex elicited by 50 ml rapid inflation (if necessary, in 50-ml aliquots up to 150 ml).
3. Fixed-volume (50 ml) water-filled rectal balloon expulsion test[38,39,44,45] in the seated position on a commode. Abnormal expulsion is defined as failure to expel within 1.0 minute of effort for men and 1.5 minutes of effort for women.[46]
4. Whole-gut transit study using serial (different shaped) radio-opaque markers over 3 days, with a single, plain radiograph at 120 hours.[47,48]

5. Fluoroscopic evacuation proctography using rectal installation of barium porridge to defaecatory desire threshold (or a maximum of 300 ml) and evacuation on a radiolucent commode[33,35–37,49] with pre-opacification of the small bowel (for enterocele). Radiation dose, proportion of contrast evacuated and time taken are recorded, as well as 'functional' features (i.e. pelvic floor dyssynergia) and 'structural' features (e.g. rectocele, enterocele and intussusception) deemed obstructive to defaecation.[38,43] Although magnetic resonance proctography is now used in some UK centres, with the advantage of no radiation dose, it was not widespread at the time of developing the CapaCiTY programme. There are also differences in sensitivity between fluoroscopic and magnetic resonance proctography, especially if the latter is carried out on a supine patient,[50] that could prove difficult for standardisation.

Standardised radiophysiological investigations were performed if results were not already available for participants from tests in the preceding 12 months. In some participants, individual missing investigations were performed. Routine NHS practice (e.g. 10-day NHS rule related to menstrual cycle) was applied in respect of women between menarche and menopause. Participants who could potentially be pregnant had a serum or urine pregnancy test performed as per routine care. Participants were given the results of investigations by the physiologist or radiologist.

Programme outcomes

A common 'standardised outcome framework' was used throughout. All questionnaires contained written instructions to be completed by the participant in an undisturbed environment without prompting. Online and postal options were provided for participants who chose not to attend in person.

The plan at the start of the programme was that all outcomes would be recorded for each intervention at baseline, 3 months and 6 months before participants could progress to a further intervention WP. For participants not changing therapy, further outcomes were recorded at 6-month intervals to the end of the programme (to a theoretical maximum of 4 years). Participants who progressed from one intervention to another had a new 'baseline' recorded on recruitment. In practice, few participants progressed from one WP to another and follow-up was limited by delays in recruitment to a maximum of about 18 months.

Primary clinical outcome

Patients with CC complain of a multitude of symptoms including infrequent defaecation, pain, bloating, straining, passage of hard stool, incomplete evacuation and systemic symptoms. The relative importance of these varies between patients so that a single symptom, such as bowel frequency, does not adequately describe treatment effect in a population.[51] Symptom diaries have a poor record as primary outcome measures, suffering from incomplete data, retrospective completion, tolerance or sensitisation.[52,53]
A number of composite scoring systems have been developed, but only one, the Patient Assessment of Constipation Quality Of Life (PAC-QoL), has been robustly developed and psychometrically validated to a high level, including a comprehensive assessment of effect size.[54–56] The PAC-QoL includes 28 items covering four domains, each item is scored (0–4 points) and items and domains are aggregated to a composite score (0–4 points).

Minimum clinically important differences have been defined for PAC-QoL scores and informed an analysis of responders to treatment. Treatment effects have been characterised using cumulative distribution curves and a 1.0-point reduction has been confirmed as a robust measure of a responder.[57] Furthermore, a minimum clinically important difference can be defined by a 10% change (i.e. 0.4 points in the scale), as reported broadly in the literature. These definitions were used to ensure that the primary outcome measure in each trial was based on magnitude, risk and cost of intervention.
Thus, for trials 1 and 2, a $\geq$ 0.4-point reduction in PAC-QoL score was considered to be a minimally important mean difference between groups, whereas in CapaCiTY trial 3 (surgery) a $\geq$ 1.0-point difference was chosen to reflect the more costly and potentially harmful intervention posed by surgery.

Secondary clinical outcomes

Given the questionnaire format of most available CC outcome assessments and multiple time points of assessment, we carefully selected and justified each outcome to keep the number and length of assessments to an achievable level (for compliance). The choice of Patient Assessment of Constipation Symptoms (PAC-SYM) and Measure Yourself Medical Outcome Profile 2 (MyMOP2) was specifically informed by qualitative research performed during our NIHR programme development stage on 50 participants with CC:

- PAC-QoL score – binary responder analyses using 0.4-point and 1.0-point cut-off points
- PAC-SYM score – individual domains and total score (as continuous variables)
- 2-week patient diary (for 2 weeks prior to each assessment) to record bowel frequency and whether or not each evacuation was 'spontaneous (no use of laxatives) and/or complete'; the journal also captured concurrent medication, health contacts and time away from normal activities (including work) since the patient's last visit
- a validated patient problem-specific measure, MyMOP2, which incorporates the two worst volunteered symptoms and a measure of well-being[58] (lower scores represent less symptomatology)
- a validated QoL cost-effectiveness questionnaire – EuroQol-5 Dimensions (EQ-5D), EuroQol-5 Dimensions, five-level version (EQ-5D-5L), and EuroQol Visual Analogue Scale (EQ-VAS)[59] (higher scores indicate better QoL)
- Patient Health Questionnaire-9 items (PHQ-9)[60] – nine items measuring level of depression (lower scores indicate less depression)
- Generalised Anxiety Disorder-7 (GAD-7)[61] scale (lower scores indicate less anxiety)
- avoidant and 'all or nothing' behaviour subscales of the Chronic Constipation Behavioural Response to Illness Questionnaire (CC-BRQ)[62] and Brief Illness Perception Questionnaire for Chronic Constipation (BIPQ-CC)[63] (specific analyses required for interpretation)
- global participant satisfaction (five-point scale from 'not at all satisfied' to 'completely satisfied') and a global participant improvement score (0–100% visual analogue scale) comparing how the participant feels today compared with before the study (higher scores indicate greater satisfaction).

Health economic outcomes

Resource use at the participant level was captured using trial case report forms (CRFs) at scheduled clinical visits and contacts. Intervention costing was specific to each trial and was detailed in the reporting of findings. Assessments were carried out at 0, 3, 6 and 12 months' follow-up, augmented by telephone calls (every 12 weeks for the CapaCiTY trial 3). Participant use of prescription drugs related to their condition was recorded and costed using Prescription Cost Analysis (PCA) data.[64] Health service contacts were recorded by asking participants to recall GP, district nurse, pharmacy, accident and emergency department (A&E), outpatient and inpatient visits. Health-care resource use was costed using published national reference costs. Individual patient costs were estimated in 2018 Great British pounds (GBP) as the sum of resources used weighted by their reference costs. Time away from work or usual activities was recorded and costed using national average weekly earnings,[65] contributing to a broader societal costing (*Table 1*).

Generic health-related QoL was assessed using the EQ-5D questionnaire: a participant-completed two-page questionnaire consisting of the EQ-5D-5L and the EQ-VAS. The EQ-5D-5L includes five questions addressing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each dimension assessed at five levels, from 'no problems' to 'extreme problems'. EQ-5D-5L scores were converted to health status scores using the mapping function developed by van Hout *et al.*,[71] providing a single health-related index including 0 (death) and 1 (perfect health), for which negative scores are possible for some health states. Scores were captured in trial CRFs during clinic visits or contacts at baseline, 3 months, 6 months and 12 months for CapaCiTY trials 1 and 2, and at 12-week intervals from the screening visit up to 72 weeks for CapaCiTY trial 3. Using the trapezoidal rule, the area under the curve (AUC) of health status scores was calculated, providing participant-level quality-adjusted life-years (QALYs) estimates for the cost-effectiveness analyses. Because AUC estimates are predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates were adjusted for baseline scores in regression analyses.

TABLE 1 Unit costs (£, 2018) applied to patient resource use

Resource	Unit	Cost (£)	Source
Health-care contacts			
GP	Per visit	39.00	PSSRU[66]
District nurse	Per visit	41.00	[a]PSSRU[67]
Pharmacist	Per visit	14.00	NHS CPCS[68]
A&E	Per visit	114.00	NHS Improvement[69]
Outpatient	Per visit	135.00	PSSRU[66]
Inpatient	Per visit	631.00	PSSRU[66]
Other resources			
Prescription drugs	Per item	[b]	NHSD-PCA[70]
Time off work	Per day	92.00	ONS[65]
CapaCiTY trial 1			
INVEST	Per procedure	462.00	
Staff time	Per procedure	192.00	NHS Improvement[69]
Anal manometry	Per test	50.00	Personal communication[c]
Rectal sensation	Per test	4.00	Personal communication[c]
Balloon expulsion test	Per test	4.00	Personal communication[c]
Gut transit study	Per study	66.00	NHS Improvement[69] and personal commmunication[c]
Evacuation proctography	Per test	141.00	NHS Improvement[69] and personal commmunication[c]
Cleaning/sterilisation	Per procedure	5.00	Personal communication[c]
Habit training (with/without biofeedback)			
Training sessions	Per hour	135.00	PSSRU[66]
Biofeedback	Per session	70.00	[d]
CapaCiTY trial 2			
Low-volume TAI	Per use	3.93	[e]NHSD-PCA[70]
	Per 30-day use	118.00	[e]NHSD-PCA[70]
High-volume TAI	Per use	7.57	[f]NHSD-PCA[70]
	Per 30-day use	227.00	[f]NHSD-PCA[70]
Training/support sessions	Per hour	135.00	PSSRU[66]
CapaCiTY trial 3			
LapVMR surgery	Per procedure	4941.00	NHS Improvement[69]

CPCS, Community Pharmacist Consultation Service; NHSD-PCA, NHS Digital Prescription Cost Analysis; ONS, Office for National Statistics; PSSRU, Personal Social Services Research Unit.

a Item reflated to 2018 costs following table 15 in *Unit Costs of Health and Social Care 2018*.[66]

b Because of incomplete recording of prescribing data, in each instance the *British National Formulary* chemical name was identified and the net ingredient cost per item was applied assuming full usage at typical dose in the follow-up period. This provided an upper bound on prescribing costs.

c S Mark Scott, Queen Mary University of London, 2020, personal communication.

d Assuming a £18,000 cost for high-resolution manometer with a 7-year life, 200 uses per year, annual warranty and catheter replacement at £11,000, annual service contract at £2700, future costs discounted at 3.5% and £5 sterilisation/cleaning cost per use [Charlie Birkett, LABORIE/Medical Measurement Systems B.V. (Enschede, the Netherlands), personal communication].

e Qufora® IrriSedo Mini (low-volume) system (MacGregor Healthcare Ltd, Tranent, UK): £118 (30 days), £3.93 per day.

f Qufora IrriSedo Cone (high-flow) system (15 irrigation set) (MacGregor Healthcare Ltd): £101.66 (15 days); Qufora IrriSedo Cone accessory set: £59 (additional 15 days), £5.35 per day. Peristeen® Anal Irrigation System (high volume) (Coloplast A/S, Humlebæk, Denmark): £76.90 (90 days); Peristeen® Anal Irrigation System accessory unit: £134.02 (15 days), £9.79 per day. The system used was not recorded, so an average of the systems was assumed.

Patient and health-care professional experience

Qualitative data were obtained to aid the interpretation of outcomes and the development of an authoritative clinical pathway that recognised informational needs of both clinicians and patients. Face-to-face, digitally recorded, semistructured interviews (duration up to 1 hour) were conducted by an experienced nurse with a social science background and involved a purposive, diverse sample of patients and health-care professionals throughout the programme, with participant recruitment reflecting a range of ages, geographical locations and, when possible, other pertinent attributes such as ethnicity and sex, continuing until data saturation when no new themes emerged. All participants were told that they might be invited for interview when they were informed about each trial, but provided separate informed consent for interview (in those agreeing to be approached). A topic guide for each interview, informed by existing literature and patient advisors, was developed and piloted prior to commencement.

Adverse events and other work package-specific data

Adverse events were recorded throughout the programme using an AE log to record the nature, seriousness, causality, expectedness, severity, relatedness and outcome. All serious adverse events (SAEs) that were related or unexpected were reported to the sponsor, REC, quality assurance manager and local research and development (R&D) departments and the participant followed-up until conclusion. Safety was monitored by the Data Monitoring and Ethics Committee (DMEC) and reported to the REC in the annual progress reports. Other important data such as treatment logs and perioperative courses were WP specific.

Common analytical framework

General

The Pragmatic Clinical Trials Unit (PCTU; a UK Clinical Research Collaboration registered and NIHR-funded clinical trials unit in the Institute of Population Health Sciences, Queen Mary University of London) managed the three trials, including the development and management of secure databases in accordance with standard operating procedures. Automated validation checks were carried out at source data entry and further checks were performed on receipt by the study statistician and data manager. Data queries were addressed to the data manager and participating centres as appropriate. The centrally held database was locked for analysis once the data quality and completeness were assured and on sign-off of the final statistical analysis plan (SAP).

Sample size calculations

Detailed individual justifications for each trial are included in *Appendix 1*. In brief, sample sizes were calculated using the primary clinical outcome: change in PAC-QoL score based on pre-defined scalar changes. All calculations were performed at 90% power at a 5% significance level and, thence, allowed for 10% drop-out after randomisation.

Baseline characteristics

Numbers and percentages of patients with important baseline characteristics are presented by trial group. Continuous variables (e.g. age) are summarised by treatment group using mean and SD [median and interquartile range (IQR) if non-normally distributed]. No statistical testing was performed.

Clinical outcomes

All analyses were performed by the study statistician after the SAP was reviewed by the DMEC and signed off by the chief investigator and senior statistician. Although exact analyses for each trial differed according to study design, primary outcomes were analysed on an intention-to-treat (ITT) basis at defined time points (3 or 6 months) using linear mixed regression models [using Stata 14.2 (Stata Corp LP, College Station, TX, USA) xtmixed] with a random effect for centre and fixed effects for intervention, sex, baseline PAC-QoL score and breakthrough medication. Secondary outcomes were analysed on an ITT basis. For each outcome, descriptive statistics (as appropriate) by trial group are presented; continuous variables (e.g. PAC-QoL score) are summarised by treatment group using mean, SD, median and IQR. For categorical variables, numbers and percentages of patients reporting each

response option were presented by trial group. Given the lower than target number of patients recruited to the trials, adjusted analyses were performed on PAC-QoL-derived secondary outcomes in CapaCiTY trial 1 only (logistic regression models for categorical outcomes). Unadjusted treatment differences and respective 95% confidence intervals (CIs) are presented for all other secondary outcomes. Results obtained using the CC-BRQ and BIPQ-CC have been omitted pending further analysis.

Subgroup analyses

Originally planned subanalyses were restricted after poor recruitment to a small number of specific analyses for major baseline characteristics in the CapaCiTY trial 1 only. A p-value of < 0.05 was taken to indicate statistical significance.

Cost-effectiveness

The economic analysis of the three interlinked CapaCiTY trials followed ITT principles and a prospectively agreed analysis plan. Using the standardised outcome framework for each trial, treatment effects were summarised at the patient level as overall cost and QALYs. Within-trial patient cost-effectiveness analyses were conducted comparing alternative treatments in each trial. Primary analyses took an NHS perspective.[72]

Follow-up of trial participants is problematic, particularly over longer periods, making incomplete data a routine challenge. Consequently, the planned base-case analysis for each trial assumed the use of multiple imputation to account for missing data. For each trial, the base-case analysis is presented as the imputed and adjusted within-trial incremental costs and QALYs gained. Supportive sensitivity analyses included participants with complete data; unplanned sensitivity analyses are added if informative. Imputation and estimation were conducted according to good practice guidance[73] using the multiple imputation framework in Stata. Multiple imputation provides unbiased estimates of treatment effects if data are missing at random (MAR) (i.e. causes of missingness are captured in observed variables). This assumption was explored in the data using logistic regression of the missingness of costs and QALYs against baseline variables.[74] Patient prognostic variables and trial stratification variables were assessed as potential missingness predictors for use in the imputation, which included outcome measures and costs (at each time point) as predictors and imputed variables. Imputation models used fully conditional (Markov Chain Monte Carlo) methods (multiple imputation by chained equations), which are appropriate when correlation occurs between variables. Multiple imputation 'draws' each provide a complete data set, which probabilistically reflects the distributions and correlations between variables. Burn-in traces for imputation variables were visualised to assess the independence of draws. Predictive mean matching drawn from the five k-nearest neighbours (k-NN) was used to enhance the plausibility and robustness of imputed values, as normality may not be assumed. Analysis of multiple draws was conducted with Stata's multiple imputation framework providing estimation adjusted for Rubin's rule.[75] In the imputation, missing costs and EQ-5D-5L scores were imputed for each period of follow-up and aggregated to overall patient costs and QALYs for each draw. All imputed variables acted as predictive variables, supplemented by trial baseline variables if significant and plausible predictors of missingness. Analysis of costs and QALYs was conducted primarily using bivariate regression. Multiple imputation estimation models were bootstrapped to provide non-parametric estimates. To minimise the information loss of finite imputation sampling, the fraction of missing information (FMI) was used to ensure that the number of imputed draws exceeded the FMI percentage. The distributions of imputed and observed values were compared to establish the consequences of estimation.

The (bootstrapped) median incremental cost-effectiveness ratio (ICER) and CI were estimated from the bivariate analysis. Value for money was determined by comparing the ICER with two willingness-to-pay (WTP) thresholds: the NICE-recommended upper threshold for 'regular' approvals of £30,000 per QALY[76] and a lower value of £15,000 per QALY, reflecting uncertainty about the true value appropriate to the NHS.[77] The chosen threshold represents the WTP for an additional QALY: an intervention with a lower ICER value than the threshold could be considered cost-effective for use in the NHS. To assess the robustness of findings, base-case assumptions were explored using a range of supportive sensitivity analyses.

Net monetary benefit (NMB) succinctly describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at (or up to) the same WTP threshold. It is calculated as:

$$\text{NMB} = \text{QALY} \times \text{threshold} - \text{cost}, \quad (1)$$

where NMB is estimated across a range of WTP thresholds such as from £0 per QALY to £100,000 per QALY. Where an intervention ICER is cost-effective (i.e. lower than the WTP threshold) the incremental NMB will be positive. NMB is routinely estimated from a bivariate regression to help generate a cost-effectiveness acceptability curve (CEAC). The CEAC visualises the likelihood that treatments are cost-effective as the WTP threshold varies.[78] Univariate regression of NMB has several advantages over the bivariate approach: it may be more robust approach with sparse data; it transforms the cost/outcomes data from a ratio into a continuous variable, allowing for easier manipulation and interpretation; it manages the correlation between costs and QALYs; it easily manages covariate imbalances; and repeated estimations explore the WTP threshold.[79] However, it does not allow the cost-effectiveness plane to be visualised, and the univariate distribution varies by threshold. Univariate regression was used as a confirmatory analysis where patient numbers were low or distributions were highly non-normal.

The expected value of perfect information (EVPI) is the upper limit of the value to a health-care system of further research to eliminate uncertainty.[80] Findings from cost-effectiveness analyses remain uncertain because of the imperfect information they use. If a wrong adoption decision (e.g. to make a treatment available) is made, this will bring with it costs in terms of health benefit forgone: the NMB framework allows this expected cost of uncertainty to be determined and guide whether or not further research should be conducted to reduce uncertainty.

Analyses and modelling were undertaken in Stata 16.1 using the portal provided at Queen Mary University of London. Reporting follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[81]

Patient experience

Interviews were digitally recorded, anonymised, transcribed verbatim and analysed using a pragmatic thematic analysis. Data analysis was developed as outlined by Fereday and Muir-Cochrane[82] in the first instance by mapping key concepts derived from the transcripts ('charting') and extracting emergent themes from the transcripts. The topic guide was used for the pre-determined codes and supplemented with additional codes that arose from the data. The final analysis combined inductively and deductively derived codes. The qualitative researcher (Tiffany Wade) conducted independent analyses and then compared and refined resulting codes and themes in discussion with the qualitative research study lead (CN). Three members of the patient and public involvement (PPI) panel were shown the qualitative results and participated in an online discussion to refine the messages. Emergent themes formed the basis of analytical interpretation. Challenges to delivering the three trials were also enquired about during the qualitative interviews with participants and research staff, using the qualitative methods described.

Patient recruitment

Challenges to recruitment

Recruitment was poor and negatively affected the whole programme (i.e. all three trials). This reflected several issues with the process and some of the design. Thus, the programme as a whole suffered from the following:

- Long-term staff [i.e. specialist NHS nurses and Clinical Research Network (CRN)-funded research nurses] sickness and retirements and difficulty in recruiting staff led to shortage of staff to deliver interventions. This was reflected by significant recruitment only at sites where research staff from the directly funded core research team took over delivery (e.g. Barts and the London School of Medicine and Dentistry, Queen Mary University of London, in CapaCiTY trial 1 and County Durham and Darlington NHS Foundation Trust in CapaCiTY trial 2).

- R&D delays to get the study up and running at many sites (range 6–9 months), with five sites never opening.
- Lack of funding to cover excess treatment costs (ETCs) [e.g. high-resolution anorectal manometry (HRAM) devices; Clinical Commissioning Groups (CCGs) to allow prescription of irrigation kits].
- Recruitment targets too high, demotivating staff and pressurising them to start recruitment before they were prepared (according to interviews).
- Some treatments were available as part of clinical practice immediately if patients refused entry into research, and with some delay if patients agreed to participate. Patients often had a significant burden of symptoms and were unwilling to delay treatment.

Other issues were trial specific. In CapaCiTY trial 1, delays due to infection control variations in approval of HRAM protocol and device cleaning (e.g. local views differed from published national standards and would require the purchase of expensive sterilisation equipment) hindered INVEST. Trial 1 also suffered criticism that the number of outcome questionnaires may have been off-putting to some patients (see *Work programme 5*, *Patient and public involvement*). In CapaCiTY trial 2, we underestimated the number of patients who would not be willing to try the irrigation device and the additional staff time above clinical need, making staff reluctant to recruit (both points highlighted in interviews). CapaCiTY trial 3 was seriously hindered by the evolving serious mesh controversy on national and international media.[83] Patients became unwilling to try the intervention and some hospitals were instructed by their lawyers to stop the intervention. A further problem in CapaCiTY trial 3 related to NHS bed pressures: the stepped-wedge design meant that one group of patients was randomised to have surgery caried out in 4 weeks. Some sites were unable to secure a bed in this time frame even with proscribed tolerance.

We took a number of measures to try to mitigate these issues:

- We provided almost all sites with refresher site initiation visits and guidance in reviewing referral letters to identify suitable patients.
- We provided all sites with a refresher investigator meeting in December 2017 to get all research staff together from all our sites with the aim to provide them with refresher training on protocol, exchange experience on overcoming recruitment barriers and encourage everyone to recruit.
- We changed the design of the studies in January 2016 to shorten the time between the follow-up visits from 24 months to 12 months to lessen the burden of the follow-up visits on both patients and research staff, and removed two lengthy questionnaires to reduce file size.
- We made protocol amendments to make the protocol more compatible with routine practice where possible.
- We provided sites with support in data entry and administrative work, which would free up the research nurse to do the screening and recruitment.
- We launched an advertising campaign in summer 2016 to find suitable patients through newspapers.
- We provided HRAM devices to sites on loan in an effort to help sites meet the requirements of study device (CapaCiTY trial 1). We undertook competitive procurement and assisted sites with business cases to secure funding for HRAM equipment.
- We secured funding from irrigation device company McGregor Healthcare Ltd (Macmerry, UK) to sponsor sites affected by the lack of prescription funding (CapaCiTY trial 2).
- We engaged with NIHR to try to encourage CCGs to meet their obligations to fund ETCs. We had letters from the Department of Health and Social Care in this regard but both it and the CRN were unable to mandate ETCs (CapaCiTY trial 2).
- We requested recruitment extensions for all three trials in an effort to boost recruitment.
- We regularly presented at national speciality meetings (e.g. the Pelvic Floor Society).
- We made use of incentives – prizes, a newsletter, social media and professional development opportunities.

Final programme recruitment

A total of 275 patients was recruited across three trials, representing a major shortfall in relation to the required cumulative sample size ($n = 808$). These patients were recruited from a total of 733 screened (37.1%); this recruitment rate was lower than the 50% recruitment rate we anticipated. About half of screen failures were due to failed eligibility and about half were due to the patient declining. There was also a problem of patient retention in all trials, with higher than anticipated drop-out rates before primary outcome (actual range 11–43% vs. anticipated range 20%).

A total of 90% of participants were female (100% in CapaCiTY trial 3) and participants had a mean age 45 years (IQR 33–57 years). The majority (70%) of participants were of white ethnicity. Baseline phenotyping indicated high levels of comorbidity in > 70% of patients and a history of previous abdominal and pelvic surgery in > 50%. In terms of other risk factors, psychiatric diagnoses (insufficient for exclusion) and joint hypermobility were each present in ≈ 20% of patients. Approximately two-thirds of participating women were parous. Although the criteria for chronicity of constipation was 6 months' duration, mean duration was 6 years and almost all patients with CC had constipation that proved intractable to lifestyle modification and laxatives, which was reflected by referral pattern: 80% of referrals were from secondary or tertiary care. Almost 20% had also failed prokinetic therapy. Symptom burden was high, with mean PAC-QoL and PAC-SYM scores of > 2.0 points at baseline. In addition, > 50% of patients had faecal incontinence symptoms, > 30% had urinary symptoms and > 20% had pelvic organ prolapse symptoms (100% in CapaCiTY trial 3).

In CapaCiTY trial 1, data from the PHQ-9, which measures depression, showed that 32.9% of participants scored > 9 points, suggesting that one-third of the sample would meet case criteria for major depressive disorder (MDD). A further 33% had scores indicative of mild depression, suggesting that, overall, around two-thirds of the sample were distressed or depressed. This compares with a point prevalence of MDD in the general population of 5%. The prevalence of MDD is, on average, at least twice as high in people with chronic medical diseases than in those without a chronic medical condition, but, even taking this into account, the rates in the current study are at the high end.[84] The findings for anxiety were similar, with one-third of the cohort (33.6%) scoring above the GAD-7 cut-off point for an anxiety disorder, and a further 25.1% reporting mild symptoms of anxiety.

Interview participants

A total of 45 patients and 23 staff members were interviewed:

- CapaCiTY trial 1. A total of 24 participants (men, $n = 3$; women, $n = 21$) were interviewed: nine participants were allocated to INVEST and 15 participants were allocated to no INVEST, to elucidate the experience of undergoing tests and being given an explanation of results or their feelings about not being tested; 11 participants were allocated to HT and 13 participants were allocated to HTBF, both improved and not improved (at 6 months) for perceptions of treatment. A total of 15 staff members were interviewed: five therapists involved in HT/HTBF to determine the comparative ease of delivery of the two therapies, three research nurses, four CapaCiTY research team members, one biofeedback physiologist, one clinical trials associate and one trainee clinical scientist.
- CapaCiTY trial 2. A total of 11 patients (men, $n = 4$; women, $n = 7$) undergoing TAI were interviewed: seven received high-volume TAI, three received low-volume TAI and one received both high-volume and low-volume TAI. Most ($n = 10$) patients were continuing to use TAI at the time of interview; however, one had discontinued use by the interview date.
- CapaCiTY trial 3. A total of 10 patients (all female) were interviewed. Nine patients were interviewed ≈ 1 year after their lapVMR to gain an understanding of what their experiences were prior to, immediately after and 1 year after the operation. One patient who declined surgery was also interviewed. A total of eight staff members (i.e. three surgeons, three research nurses, one gastroenterologist and one research team member) were also interviewed about both the interventional and research element of the study.

Work programme 2: CapaCiTY trial 1 – randomised trial of habit training compared with habit training with direct visual biofeedback in adults with chronic constipation

Specific background and rationale

In most UK practices, patients with CC are first referred to specialist nurses for a variety of nurse-led behavioural interventions to improve defaecatory function. A range of cohort studies,[85] RCTs,[86–91] reviews,[92] guidelines[93] and meta-analyses[94] attest to the general success of this approach. However, opinion varies greatly concerning the complexity of intervention required and UK survey evidence (performed as part of this programme) indicates that there is remarkable variability of practice.[95]

A simple form of behavioural therapy is habit training. This involves optimising dietary patterns to maximise gastrocolic response and the morning clustering of high-amplitude propagated colonic contractions that propel contents towards the rectum for subsequent evacuation. 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 and balloon expulsion exercises are often included.

More complex forms of therapy include instrument-based biofeedback learning techniques.[85–91] Favoured in the USA and by about half of UK centres, these provide direct visual computer-based biofeedback of pelvic floor activity. Although small RCTs suggest an additive value of biofeedback over habit training alone in the management of selected patient subgroups of CC (e.g. dyssynergic defaecation),[87,96–98] there has been no multicentre or adequately powered RCT in unselected patients, despite the uncertainty having significant resource implications. Aside from the issue that there is now considerable disagreement regarding the very diagnosis of dyssynergic defaecation (including from our own study using HRAM),[99] most publications advocating biofeedback have come from specialist centres with considerable 'investment' in these techniques, with reports much less favourable when biofeedback is the 'de-vested' comparator.[100,101] The controversy following a Cochrane review that drew attention to the limitations of the evidence base[102] attests to the polarity of opinion on this subject and the need for a more definitive (i.e. a larger, higher-quality) RCT.

This underpinned our first trial-specific research question:

- In unselected (i.e. no-INVEST group) adults with CC, is HTBF more clinically effective than HT as measured by PAC-QoL score at 6 months' follow-up?

A further unanswered question regards the utility of behavioural therapies in different subgroups of patients with CC. Well-regarded international consensus (e.g. the Rome VI Criteria)[103] supports a view that biofeedback significantly benefits only a subgroup of patients with a form of functional defaecation disorder termed 'dyssynergic defaecation' (see *Figure 1*). This poses the question whether or not further tests are required at an early stage (i.e. before behavioural therapy to select patients for biofeedback). There are significant differences of expert opinion on this subject: some advocate early

complex and expensive investigations to guide treatment in most patients,[8] whereas others advocate undertaking such tests only in resistant cases or in those progressing to surgery.[104] The advantage of guiding treatment[105,106] is balanced against the invasive nature of some tests, radiation exposure, embarrassment and cost (≈ £600–1200 NHS tariff); most also necessitate an escalation of care (i.e. from secondary to tertiary centre). The need to resolve this question has been consistently highlighted[38,107] but, to our knowledge, prior to the programme no RCT had stratified treatment selection on this basis.

This underpinned our second trial-specific research question:

- Is the impact of such specialist-led interventions improved by stratification to HTBF or HT based on prior knowledge of anorectal and colonic pathophysiology using INVEST as measured by PAC-QoL score at 6 months follow-up?

Both research questions were embedded in a single experimental design with three parallel trial groups and required a total sample size of 394 patients. For a full description of this trial, including interventions, trial-specific design procedures and all results and analyses, see *Appendix 1*. Only the main results and conclusions are summarised in this report.

Results

Recruitment started on 26 March 2015 (first intervention 21 May 2015) and ended 30 June 2018. A total of 182 participants (of the target 394 participants) were randomised out of 502 screened (36.3%) from 10 sites. Two sites opened but failed to recruit; the remainder randomised between 7 and 71 participants. A total of 68 participants were randomised to HT, 68 participants were randomised to HTBF and 46 participants underwent INVEST-guided therapy (HT or HTBF based on results) [the Consolidated Standards of Reporting Trials (CONSORT) flow diagram is shown in *Figure 2*]. A total of 178 participants provided PAC-QoL data at one or more time points (*Figure 3*). The primary outcome (PAC-QoL score) was available at both baseline and 6 months for only 103 participants. There was no evidence of an additive effect of HTBF over and above HT (*Table 2*).

A range of secondary outcomes covering symptoms and QoL improved in both the HT group and the HTBF group (e.g. mean PAC-SYM score reduced from 2.2 points at baseline to 1.5 points at 6 months and weekly laxative use reduced fourfold). Interventions led to small reductions in depression but no significant differences between the intervention types. Overall, about 65% of participants were globally satisfied or very satisfied with both interventions and this was reflected by participant experience reported at interview (i.e. similar proportions of participants liked, and a minority disliked, both interventions for a number of reasons).

Similar results were obtained for INVEST versus no-INVEST, with no evidence of a difference in primary outcome (see *Table 2*): participants provided reasons for liking INVEST (e.g. greater knowledge of their condition and knowing that it was not 'all in their mind') and disliking the invasiveness and embarrassment of the tests.

Given similar changes in EQ-5D-5L scores for all interventions, cost-effectiveness analyses favoured the simpler strategies (i.e. HT and no INVEST) as the dominant strategies. In both instances, cost increases were significant (HTBF vs. HT: £239, 95% CI £133 to £354; INVEST vs. no INVEST: £543, 95% CI £403 to £685) and QoL reduced (HTBF: –0.010 QALYs, 95% CI –0.053 to 0.03 QALYs; INVEST: –0.047 QALYs, 95% CI –0.093 to –0.001 QALYs). The probability that HT is cost-effective was a *p*-value of 0.83 at a WTP threshold of £30,000 per QALY.

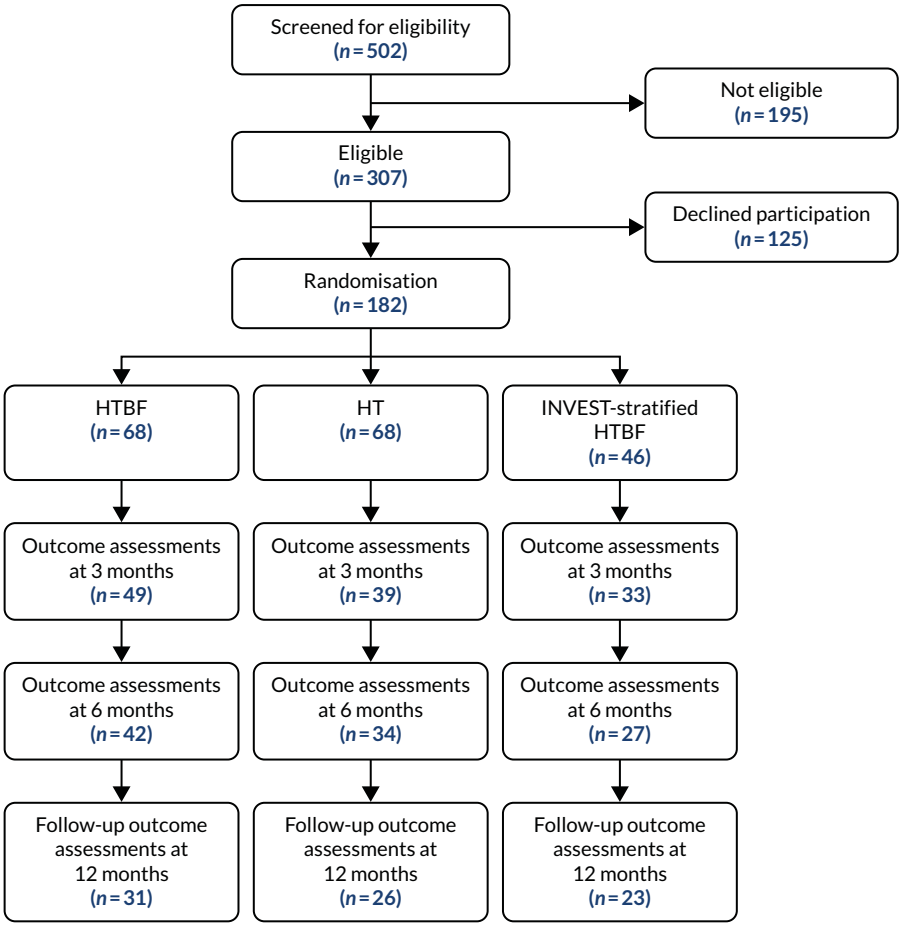

FIGURE 2 The CapaCiTY trial 1 CONSORT flow diagram.

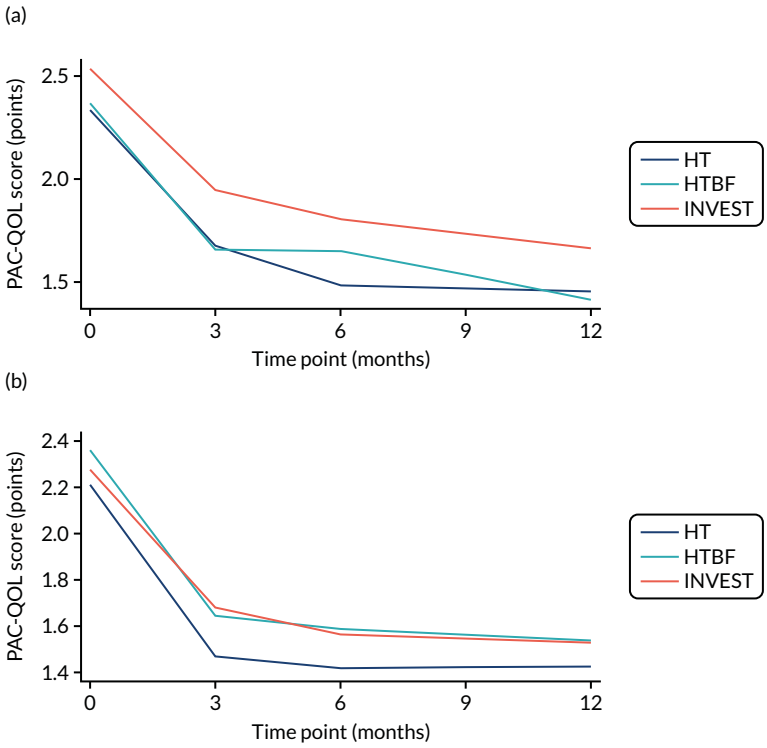

FIGURE 3 Overall PAC-QoL scores. (a) All participants ($n = 178$ at baseline); and (b) participants with no missing data to 12 months ($n = 54$). Both figure parts show reductions in score (i.e. improvement) over time.

TABLE 2 Overall PAC-QoL score by randomised group and mean differences between HT and HTBF groups and no-INVEST and INVEST groups for those included in the final analysis model

Intervention	PAC-QoL score (points), mean (SD)		Treatment difference[a] (95% CI)	*p*-value
	Baseline	6 months		
HT vs. HTBF				
HT ($n = 38$)	2.26 (0.69)	1.49 (0.85)	Reference	
HTBF ($n = 30$)	2.41 (0.81)	1.65 (1.03)	−0.03 (−0.33 to 0.27)	0.8445
No INVEST vs. INVEST				
No INVEST ($n = 68$)	2.33 (0.74)	1.56 (0.93)	Reference	
INVEST ($n = 22$)	2.36 (0.78)	1.81 (1.03)	0.22 (−0.11 to 0.55)	0.1871

a Adjusted for sex, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).

Conclusions

Taking together the results from clinical effectiveness, cost-effectiveness and patient experience data, the following conclusions may be drawn while accepting the major caveat of under-recruitment:

- Included adults with CC had high levels of symptom burden and long durations of symptoms that had been refractory to previous treatments and could therefore be considered 'hard to treat'. These symptoms were associated with a substantive effect on QoL and psychological well-being. Patient experience reflected the misery of the condition and fear that treatments would be ineffective.
- Our analysis of clinical effectiveness showed that all interventions trialled (i.e. HT, HTBF with INVEST and HTBF with no INVEST) reduced symptom burden and improved disease-specific QoL. The observed magnitude of these PAC-QoL score changes (≈ 0.8 points) can be considered to be clinically meaningful and represented a greater reduction than the minimum clinically important difference sought between groups by design (mean change 0.4 points). The findings from the primary outcome were coherent with a panel of secondary outcomes, and, overall, such improvements are unlikely to have occurred spontaneously in a condition that is generally considered chronic and stable.
- Confidence intervals rule out clinically important differences between HT and HTBF for the primary outcome and all main secondary outcomes. The same was true of INVEST and no INVEST.
- Standardised specialist-led habit training alone and no INVEST are strongly supported by cost-effectiveness analyses. Despite under-recruitment (182 out of a planned 394 participants), participant-level data provided the most robust evidence to date on the first step of care for patients referred to hospital for CC. Neither a complex specialist-led intervention (e.g. pelvic floor retraining using biofeedback) nor stratification to complex or standardised therapy based on prior knowledge of anorectal and colonic pathophysiology (INVEST) were more cost-effective than HT. Analysis suggests that HT is the dominant strategy (i.e. lower cost and greater QoL) at a WTP threshold of £30,000 per QALY.
- All procedures were safe and well tolerated by patients.
- Interviews suggested that patient experience was mixed. Some regretted not being allocated to INVEST or HTBF (because they believed that they would have less knowledge of their condition and less likelihood of treatment success), whereas others felt that the tests and biofeedback were embarrassing and intrusive. Most participants reported a positive interaction with staff and at least some symptom benefit. Most would recommend trying the intervention they received to other people with CC.
- Staff were mostly supportive, but some found that adhering to the agreed intervention protocol constrained their clinical flexibility and they would have preferred to individualise the intervention. The biofeedback element added time to consultations, or limited what they could cover in HT.

- Because these patients had significant psychological comorbidity, and there is evidence that psychological treatments such as cognitive–behavioural therapy have significant and sustained benefits on symptoms, mood and QoL in people with irritable bowel syndrome (many of whom also experience severe constipation), future work should focus on incorporating psychological methods alongside HT.[108,109]
- Taken together, the cost-effectiveness data (in the absence of differences in clinical effectiveness, patient experience and safety) promote the adoption of the simpler pathway (i.e. HT without INVEST). A revised prototype pathway is provided on this basis in the final conclusions of the synopsis (see *Figure 8*).

Reflections on work programme 2

This WP was severely hampered by poor recruitment, with many of the general challenges listed in *SYNOPSIS*. It is not the place here to repeat well-rehearsed arguments about the frailties of delivering a complex research intervention in a resource-strained NHS, but these certainly affected this trial. That noted, with the benefit of hindsight, and even after simplifying the trial design at the award approval stages, the study was probably overambitious in design. We tried to answer two research questions concurrently with one experimental design (HT vs. HTBF and INVEST-stratified vs. no INVEST-stratified treatment). This was laudable and based very clearly on nationally agreed research priorities at the time (e.g. from the American Gastroenterology Association).[93] However, it might have been better to have simplified the design to one that compared only HT with HTBF in a two-group trial without INVEST. This would have not only reduced the sample size (and general complexity) but also avoided some of the issues of equipment shortages and approvals (including infection control procedures) that delayed many centres from opening for as long as 1 year (with some never opening). We considered this option at the second review stage but felt that it was too great a departure from our original application. An alternative design (based on our qualitative data) might have been preference based. Another issue was the complexity of inclusion criteria and the number and complexity of outcome instruments. Despite PPI input at the outset, and changes made (with PPI) during the programme, outcome collection was still burdensome. Although the type of strict inclusion criteria and outcome panel we employed seem to still be the norm in recent pivotal trials, a more pragmatic (relaxed) approach to inclusion and a smaller outcome booklet would (with hindsight) have been preferable.

Despite these challenges, the trial undoubtedly brought together a fragmented community of experts from around the UK and led to the standardisation of practice. Two publications from early in the programme highlight the previous lack of understanding of what actually constitutes biofeedback[95] and what investigations tests should be performed and how.[34,110] The former was borne out by our qualitative data (i.e. many practitioners preferred to tailor their approach to each patient). The latter led to an international effort to introduce technical standards on performing and interpreting diagnostic tests of anorectal function, in which the CapaCiTY team were leaders, and these have been published.[111]

Finally, it must be recognised that, despite under-recruitment, CapaCiTY trial 1 is, to our knowledge, nevertheless the largest RCT to date in which biofeedback is one of the trialled interventions. A total of 182 patients were randomised; sample sizes in 17 previous RCTs included in a Cochrane review[102] ranged from 21 to 119 (and it is noted that the trial with 119 patients[101] was focused on surgery with biofeedback as the comparator). Therefore, it is acknowledged that among many UK practitioners there will be a sentiment that the results of CapaCiTY trial 1 do still provide an answer to a major question – namely, that the sort of specialist-led biofeedback practice advocated by a small but very vocal group of experts in the USA is less likely to work in an NHS pathway. The main points are as follows: (1) there is insufficient human resource (trained specialist nurses) and equipment (manometry catheters) to provide it (CapaCiTY trial 1 had three to four sessions; in the USA five to seven sessions are prescribed); and (2) there is a general disbelief (reinforced by the findings of the study and a prior Cochrane review)[102] that direct visual biofeedback offers much to patients over and above the panoply of approaches encompassed by HT (including holistic elements of patient support as well as didactic training) when it comes to the average patient (i.e. widespread adoption would be protracted if possible at all).

Research recommendations

The primary outcome effect size was almost identical for all groups and it is unlikely that another trial, even with a much greater sample size, would detect a clinically important difference between interventions. Certainly, the CI for the effect comparing HT and HTBF excludes the difference we initially set as the minimum clinically important difference in our sample size calculation. Thus, it is hard to recommend further investment, even with a more simplified trial design. We cannot comment on whether or not the US expert view is correct; perhaps limitation to highly selected patients with proven dyssynergic defaecation and specialist equipment in the hands of very expert medical practitioners (undertaking multiple sessions of therapy) does result in better outcomes (we did not trial this). However, we believe that this would be difficult to trial successfully in the NHS for the reasons outlined, and were it to produce the same results as CapaCiTY trial 1 it would still be unlikely to influence international opinion owing to the financial reimbursement drivers that promote the US approach. As noted, there may be rationale to include some form of psychological therapy alongside habit training for the large proportion of patients with significant psychological morbidity (akin to trials for patients with irritable bowel syndrome). This is an area for further research.

Work programme 3: trial 2 – pragmatic randomised trial of low-volume compared with high-volume initiated transanal irrigation therapy in adults with chronic constipation

Specific background and rationale

Transanal irrigation, for which there are a variety of commercially available devices, has been rapidly disseminated internationally since about 2000, first in CC patients with neurological injury[112,113] and subsequently in other groups CC groups.[114,115] Despite a lack of published data other than from small selected case series, TAI is now available on drug tariff (at a cost of ≈ £2500 per patient per annum) and is generally considered to be the next step for patients failing other nurse-led interventions. TAI has permeated the UK market without robust efficacy data and with ongoing concerns regarding longevity of treatment and complications.[112,116] Retrospective clinical audit data and review[116,117] by the applicants suggest a continued response rate after 1 year of ≈ 50%, with patients thus avoiding or delaying surgical intervention, but an accurate assessment of response rate and acceptability of this intervention required confirmation in a trial. In addition, two alternative systems for delivery of TAI exist: low-volume systems delivering ≈ 70 ml per TAI, and high-volume systems delivering up to 2 l of TAI (although typically only 0.5–1.5 l is required per TAI). The theoretical benefit of higher-volume TAI is greater efficacy – simply put, more washout. However, the low-volume system is cheaper, costing ≈£750 per annum, based on alternate-day use, compared with a cost of £1400–1900 per annum for high-volume TAI, and it may also be less traumatic and more acceptable to patients.

This underpinned our first specific research question:

- In patients with CC who have failed conservative treatment (HT or HTBF), what is the impact on disease-specific QoL of TAI initiated with a low-volume and a high-volume system measured by PAC-QoL score at 3 months' follow-up?

Transanal irrigation is an invasive therapy that requires, every day or every couple of days, insertion of the device into the anus followed by a period spent filling the rectum with fluid and then evacuating it. It is reasonable to suppose that patients would discontinue therapy that they felt was ineffective or unacceptable, or switch between low-volume and high-volume systems (permissible in the trial design).

This underpinned our second trial-specific research question:

- What is the survival rate of therapy of TAI initiated with a low-volume and a high-volume system and do patients prefer one system to another?

Both research questions were embedded in a single, pragmatic, two-group parallel design (*Figure 4*) and required a total sample size of 300 patients (150 per group). Patients used one system only (plus defined 'rescue therapies') for a minimum of 3 months. After this time point they could switch to the other system if their initial therapy was ineffective/unsatisfactory. This allowed identification of response rates to each system in the short term (3 months) and, thereafter, a comparison between treatment strategies (TAI initiated with low-volume therapy or high-volume therapy) rather than a pure comparison of the

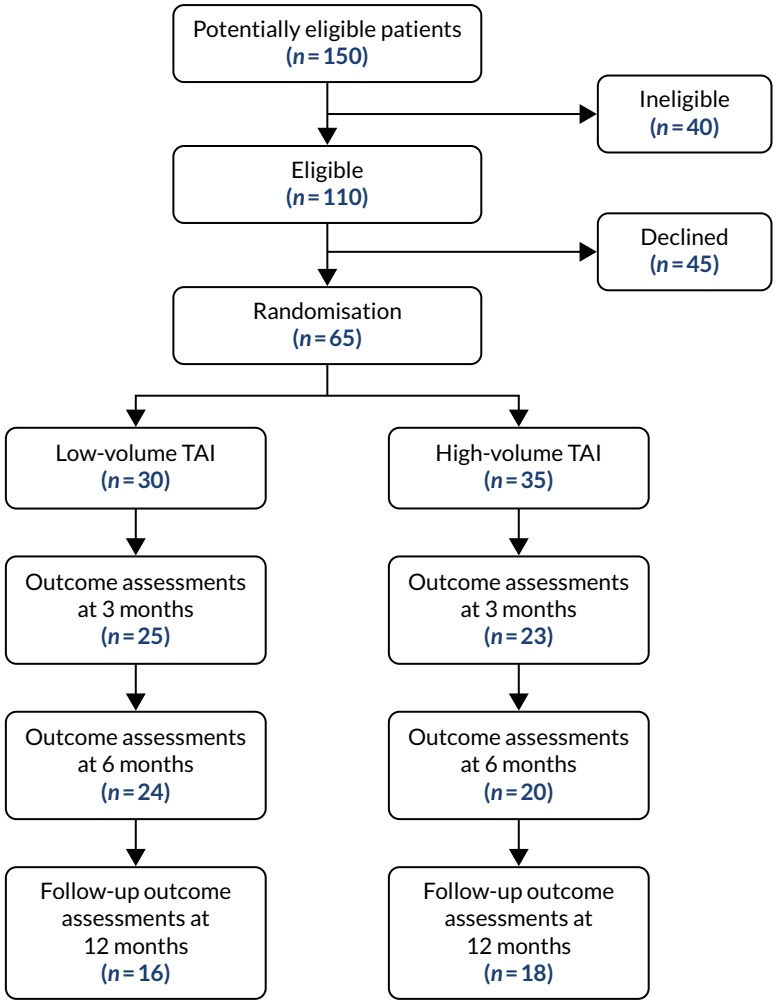

FIGURE 4 The CapaCiTY trial 2 CONSORT flow diagram.

two techniques. This was a patient-centred study design aiming to limit the time that patients spent using ineffective therapy without being allowed to try an alternative. Reasons for switching were captured qualitatively.

For a full description of this trial, including interventions, trial-specific design procedures and all results and analyses, see *Appendix 1*. Only the main results and conclusions are summarised in this report.

Results

High-volume compared with low-volume transanal irrigation

First recruitment and intervention took place on 11 November 2015; recruitment ended 30 June 2018. A total of 65 patients (target 300 patients) were randomised from 150 screened (21.7%) from seven sites. Three sites opened but failed to recruit; the remainder randomised between 1 and 33 patients, with approximately half of the patients recruited from secondary care and half recruited from tertiary care. A total of 30 patients were randomised to low-volume TAI and 35 to high-volume TAI (see *Figure 4*). The primary outcome (PAC-QoL score) was available at baseline and 3 months for only 43 patients.

At 3 months there was a modest reduction in mean PAC-QoL score from 2.4 points to 2.2 points (SD −0.2 points) in the low-volume TAI group and a larger reduction of −0.5 points in the high-volume TAI group (*Table 3*). Although this difference was not large there was consistency of findings across some of the other outcome measures. For example, global satisfaction score, global improvement score

TABLE 3 The CapaCiTY trial 2 primary outcome: PAC-QoL score, low-volume TAI vs. high-volume TAI

	Baseline		3 months		
Intervention	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Difference in means (95% CI)
Low-volume TAI ($n = 19$)	2.4 (0.8)	2.4 (1.9–2.9)	2.2 (0.8)	2.0 (1.5–2.8)	Reference
High-volume TAI ($n = 25$)	2.3 (0.7)	2.4 (1.8–2.8)	1.8 (0.9)	1.8 (1.1–2.3)	–0.37 (–0.89 to 0.15)

and EQ-VAS score showed greater improvement in the high-volume TAI group. These results were based on an ITT analysis even though two patients crossed over (from low-volume to high-volume TAI) before the 3-month outcome (possibly diluting the difference in effect).

Some further evidence of the greater benefit of high-volume TAI could be inferred from the fact that, over the follow-up period (with the majority after 3 months), 18 patients switched from low-volume to high-volume TAI but only six patients switched from high-volume to low-volume TAI, and two of these six switched back again to high-volume TAI.

Despite under-recruitment, patient-level data from the trial still provided the most robust evidence available to inform the pathway of care. Despite differences in initial purchase prices of the basic devices, initiating high-volume TAI did not increase study cost but resulted in higher patient QoL, suggesting a dominant interventional strategy (cost-effective at a WTP threshold of £30,000 per QALY; $p = 0.99$).

The interventions were generally well tolerated considering the invasive nature of the procedure. A total of 16 out of the 65 patients (25%) reported AEs, with a total of 68 AEs. Of these, 40 AEs (59%) were mild and 20 (29%) were moderate. There were six SAEs, of which three were expected. All resolved with no sequelae.

Survival rate of transanal irrigation therapy

In the absence of a sham control (impossible to devise), and with the inability to compare with standard therapy, it was reasonable to use treatment continuation as a marker of efficacy. The treatment is burdensome, and it can be argued that patients who are not receiving benefit would not continue with it. There was no encouragement from research or clinical staff for patients to continue to use ineffective therapy. The 1-year survival rate of the treatment of 76% (*Figure 5*) implied significant continued effect. A comparison of survival rate plots of low-volume and high-volume TAI that allows for crossover has not been presented at the time of publication. This analysis is planned but was outside the SAP.[118]

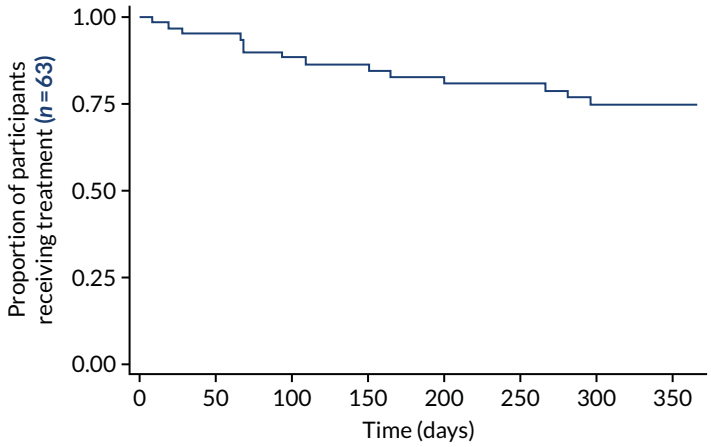

FIGURE 5 The CapaCiTY trial 2 survival rate of treatment as a surrogate of ongoing benefit: Kaplan–Meier plot for time to cessation of treatment.

Conclusions

Taking together the results from clinical, cost-effectiveness and patient experience data, the following conclusions may be drawn while accepting the major caveat of under-recruitment:

- The population studied represented a typical hospital-derived cohort of patients with severe CC that had not responded to conservative therapies.
- We did not carry out statistical significance tests owing to under-recruitment. Despite this, there is preliminary evidence that high-volume TAI may be more effective than low-volume TAI. Although effect sizes were small for both primary and secondary outcome measures (especially global improvement scores), dominant crossover from low-volume to high-volume TAI and health economic analysis point in the same direction of favouring high-volume TAI.
- Survival rate data were suggestive of a persisting benefit in the majority of patients, with three-quarters of patients still using TAI at 12 months. Overall, there were fewer patients on low-volume TAI at 12 months than on high-volume TAI. A survival rate analysis allowing for crossover is yet to be undertaken.
- Some AEs were reported, but, of six SAEs, none was related or life threatening. The most common AEs were rectal bleeding and anal pain (48 events in 16 patients).
- Despite under-recruitment, patient-level data from the trial still provided the most robust evidence currently available to inform the pathway of care. Initiating high-volume TAI did not increase overall cost (despite slightly higher basic device pricing) and resulted in higher patient QoL, suggesting a dominant interventional strategy (cost-effective at a WTP threshold of £30,000 per QALY; $p = 0.99$).
- Although cost-effectiveness base-case findings were robust to the complete-case and sensitivity analyses conducted, the findings should be treated with caution. Small absolute numbers of patients and high levels of missing data as follow-up progressed placed great reliance on the imputation process and output. As with CapaCiTY trial 1, although substantial efforts were made to deliver a robust imputation process, it not possible to prove that a MAR process has been attained. Actual level of TAI use (the predominant cost) was not directly recorded and was instead approximated from available variables.
- A final consideration in support of high-volume TAI concerns convergence. Health-care costs are similar comparing the two groups, suggesting that differences in health-care costs beyond 12 months are small. However, QoL diverges between groups over 12 months, suggesting that QALY gains may continue to accrue for some time beyond 12 months. Although speculative, any modelling of future cost and benefits would further increase the cost-effectiveness of high-volume TAI.
- Transanal irrigation often caused initial anxiety, was not always easy to learn and was time-consuming. Ongoing staff support was much appreciated, especially as results were not always immediate. Some found it of no benefit, but many persevered and found that, although not necessarily a pleasant experience, it had an impact (sometimes large) on their symptoms and QoL. Staff were possibly more enthusiastic than patients initially, and this enthusiasm was picked up by patients in some cases and helped them to persevere.

Reflections on work programme 3

Poor recruitment (65/300; 22%) was a disappointment and reduced the inferential quality of the study. As well as the usual difficulties as discussed for CapaCiTY trial 1, we failed to recognise an important constituent: that the patients offered TAI had (1) a severe burden of illness and (2) already tried all the usual conservative measures (which had failed). They were resorting to TAI often in a state of desperation. The difficulty, then, was that recruitment to the trial resulted in a delay in treatment while baseline assessments and investigations were undertaken. At the same time, patients were aware that they could access the treatment immediately if they remained outside the trial. With hindsight, it should have been clear that this would lead to difficulties. To overcome this would have required a waiting list for non-trial treatment or a pragmatic approach in which investigations and baseline diaries

were dispensed with (as they are dispensed with in emergency medicine trials). Further issues, such as the failure to obtain funding for the therapy in several UK regions, proved beyond our control despite extensive discussion with relevant CRNs and at a national level. Ironically, we received letters stating that funding would not be provided because the therapy lacked evidence from a randomised trial.

Despite gross under-recruitment, we believe that the trial provided some meaningful evidence that high-volume TAI may be more effective than low-volume TAI for the majority of patients. The CI for the effect size appeared to rule out a clinically important difference of 0.4 in favour of low-volume TAI and not in favour of high-volume TAI. This finding promotes a care pathway in which high-volume TAI might be initiated as a default for patients when there is not a compelling reason or preference for low-volume TAI. This is a useful conclusion, but it lacks identification of a more definite means of stratifying patients to one treatment or the other based on baseline phenotype. Ideally, we would have liked to study the efficacy of TAI per se, but there was no way of designing a sham control. A waiting list comparison was considered but rejected because waiting times were not long enough to provide meaningful data. A cohort design was also proposed, but the grant review panel encouraged a RCT. The appeal of considering low-volume and high-volume TAI was the ability to relate responders in the different treatment cohorts to symptoms (urge vs. no urge) and selected physiology results (notably, presence or absence of blunted rectal sensation). We could potentially have learned something about the physiology and mechanism of action of these treatments by doing this. However, with very low recruitment numbers, these additional analyses (covariates of response to each or both therapies) could not be undertaken.

It was interesting to note from the staff interviews that specialist nurses providing the treatment already had strong views that high-volume TAI was a better treatment. It is possible that some bias might have been affected by these opinions.

Research recommendations

It does not seem necessary to recommend repeating the trial on the basis of inadequate recruitment because any future trial will face many of the same challenges, even with the changes proposed here. Furthermore, a more basic question still remains: what is the value of any type of anal irrigation? There have been a significant number of retrospective observational studies and occasional prospective ones. The difficulty would be in establishing a control, as already stated here. It may be possible to develop a prospective cohort study of patients with CC that, while being monitored prospectively, might adopt TAI as an alternative to usual care. A trials within cohorts (TwiCs) design could be considered if patients would consider secondary randomisation against continuing usual care.

The qualitative evidence has been very illuminating and further analysis of this will be undertaken to understand drivers for continuing and discontinuing therapy (to guide patient selection and encourage compliance). As new equipment is developed (including devices activated by mobile telephones) there may be a desire to assess equivalence and safety. In addition, there is a need to understand the merits of contraindications such as mild colitis and pregnancy.

Work programme 4: CapaCiTY trial 3 – stepped-wedge randomised trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation

Specific background and rationale

When non-surgical therapies fail, a decision must be made about whether or not to offer surgical interventions. Decision-making is greatly influenced by local expertise, commissioning and personal enthusiasm for particular interventions[25,119,120] balanced against poor results in some patients.[25] Currently, there is large and difficult-to-justify variation in surgical practice according to need and type of procedure. The need to reduce variations in practice, based on available evidence, is a perpetual theme of national specialty group discussions, with various initiatives proposed. Multidisciplinary team (MDT) processes have been established in the UK with the aim of reducing potential for inadequately informed and potentially harmful interventions in poor surgical candidates.[25] However, when these MDT processes occur, decision-making is not helped by a near void of high-quality evidence.

At the time of starting the CapaCiTY research programme, lapVMR was considered a very effective procedure for the management of selected patients with CC. This procedure was first described for the treatment of external rectal prolapse in 2000[121–123] and then for patients with internal prolapse and/or rectocele presenting with CC.[124–131] Its popularity, based on its lesser invasiveness and perceived small detrimental effect on bowel function,[132] soared 15-fold in the UK between 2001 and 2012[133] but rapidly declined during the CapaCiTY research programme (2016 to present) when concerns regarding the use of pelvic mesh surfaced in the media[83] and the courts.[134]

The evidence for efficacy of lapVMR was limited to observational data, the majority of which derived from single-centre case series. It is clear that complications can be limited by good technique and perhaps choice of mesh, but complications will not be eradicated. Thus, it can be argued that the future of lapVMR depends not on the very small observed differences in long-term mesh complications (e.g. in 1.0–2.0% of patients) but on a fundamental evaluation of whether or not the procedure is actually clinically beneficial (i.e. whether or not these complication rates would be deemed acceptable, provided patients are consented to the risk, if the patient benefit was sufficiently large).

This underpinned the specific research question:

- In selected adults with CC who have failed conservative treatment (i.e. HT or HTBF with or without TAI) and who have high-grade internal rectal prolapse, what is the clinical efficacy of lapVMR compared with controls at short-term (i.e. 24-week) follow-up.

In addition, this WP included the delivery of a series of high-quality systematic reviews for all main surgical procedures employed to treat CC to define benefits and harms and provide prototype graded practice recommendations (including for lapVMR).

We used a stepped-wedge randomised trial design to permit observer-masked data comparisons between patients awaiting intervention and patients who have undergone surgery. Contrary to most stepped-wedge trials, individual patients (as opposed to clusters) were randomised. In brief, eligible participants were randomised to three groups with different delays before surgery (*Figure 6*). In all

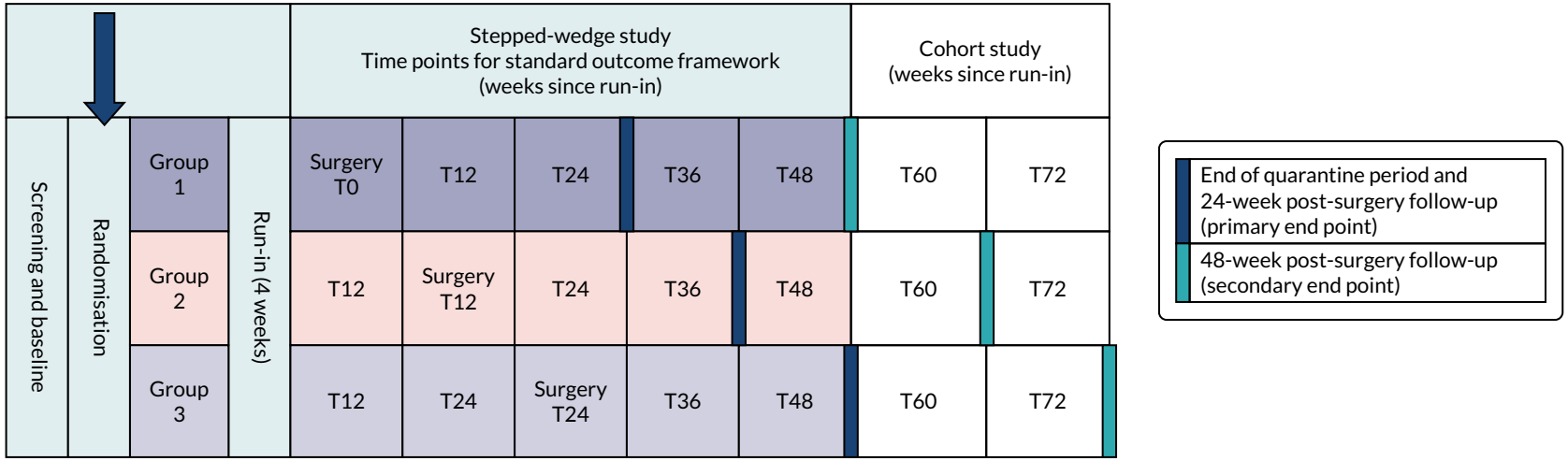

FIGURE 6 The CapaCiTY trial 3 schematic stepped-wedge design.

groups there was a period of 4 weeks post eligibility assessment to arrange the logistics of surgery [time (weeks) since randomisation (T) –4 (T–4) to T0] and ensure that patients have returned to their normal life routine after various assessments. lapVMR was performed in group 1 at T0, in group 2 at T12 and in group 3 at T24. Unavoidably, participants were aware when surgery was undertaken and thus met one of the assumptions of a stepped-wedge design (i.e. no effect of treatment expected until surgery has been performed). Efficacy outcome data were collected at equally stepped time points (T0, T12, T24, T36 and T48). PAC-QoL and PAC-SYM total scores were analysed using a mixed linear regression model, adjusting for a random effect of participant and a fixed effect of time since randomisation (see *Figure 6*). The effects of the intervention at 12, 24, 36, 48, 60 and 72 weeks post surgery were modelled as fixed effects. For example, the intervention effect at 12 weeks post surgery was included in the regression model using a dummy variable set to 1 in those cells of *Figure 6* where surgery occurred 12 weeks previously [i.e. at T12 in group 1 (when surgery was at T0), T24 in group 2 (when surgery was at T12) and T36 in group 3 (when surgery was at T24). This was the expected difference in outcome between a patient who had surgery 12 weeks previously and a patient who had not had surgery. This was similar for intervention effects at T24, T36, T48, T60 and T72 weeks post surgery. The analysis included a Kenward–Roger correction to correct for the small sample size, and was performed in Stata using the 'mixed' command with the options 'reml dfmethod(kroger)'.

The choice of design (in effect a modification of a standard, parallel-group, waiting-list control design) had several advantages. First, a stepped-wedge design is more efficient and thus improves recruitment feasibility (the major hurdle of nearly all surgical trials). Despite the multicentre approach of this study, the problems of recruitment were manifest. Simulation demonstrated that a parallel-group design required a much larger sample size than that proposed for the current study at the same power. Second, the trial design meant that there was only a one in three chance (rather than a one in two chance as in a parallel-group design) of waiting almost 6 months for surgery, which was more acceptable to patients (according to a 100-patient survey during the programme development phase). Using this design required a sample of 114 patients with 95% power (purposely chosen to reflect the magnitude and risk of intervention) at a 5% significance level.

For a full description of this trial, including interventions, trial-specific design procedures and all results and analyses, see *Appendix 1*. Only the main results and conclusions are summarised in this report.

Results

Stepped-wedge randomised trial

The first recruitment was on 1 March 2016, with the first intervention on 15 June 2016. Recruitment ended on 31 January 2019. A total of 28 patients (target 114 patients) were randomised out of 81 screened (34.5%) from nine sites. Two sites opened but failed to recruit and one site failed to randomise; the remainder ($n = 6$) randomised 1–11 patients each. Nine patients were randomised to immediate surgery, 10 were randomised to a 12 weeks' waiting time and nine were randomised to a 24 weeks' waiting time. The CONSORT flow diagram is shown in *Figure 7*. One patient was randomised but did not undergo surgery. However, this patient remained in the study on ITT principles. Two patients dropped out of the study before the primary end point and a further five failed to complete the primary outcome (PAC-QoL score at 24 weeks), which was therefore undertaken in 19 patients.

Laparoscopic ventral mesh rectopexy resulted in substantial improvement in symptoms, with the mean PAC-QoL score reducing from 2.63 points at baseline to 1.26 points at 24 weeks, and a similar reduction in PAC-SYM score from 2.24 points at baseline to 1.19 points at 24 weeks (*Table 4*). Secondary outcomes also indicated improvement over time, with PAC-QoL and PAC–SYM scores showing maintained reductions compared with baseline up to the 72-week time point (accepting potential attrition bias). Improvements in total score reflected improved scores across all domains of the instruments. Positive directional effects were observed for nearly all other secondary outcomes,

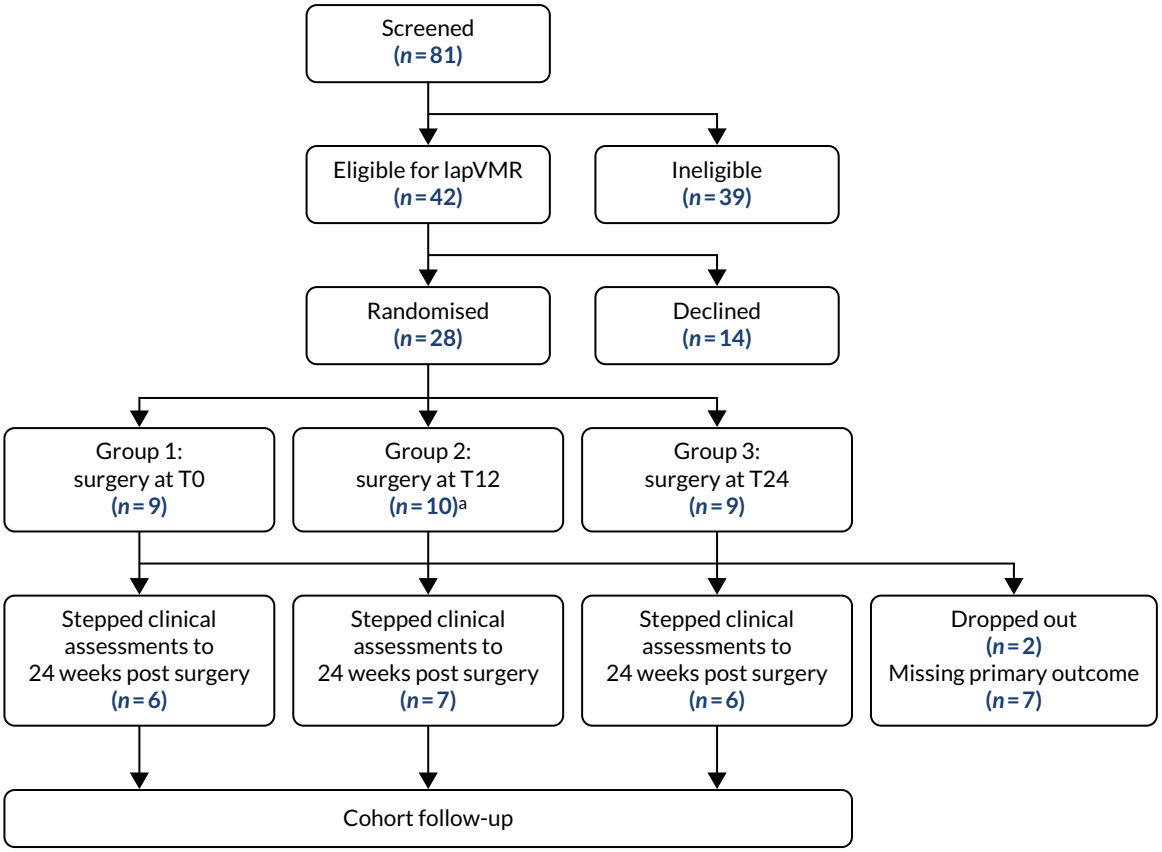

FIGURE 7 The CapaCiTY trial 3 CONSORT flow diagram. a, One patient did not undergo surgery; this patient continued to participate and was included in analysis on ITT principles.

TABLE 4 Total PAC-QoL and PAC-SYM scores at baseline and follow-up points post surgery, with 95% CI and *p*-value for change from baseline to each follow-up point

Time point	Number completing outcome evaluations	Observed mean score (points)	Estimated change from baseline score (points)	95% CI for change in score (points)	*p*-value for change in score (points)
PAC-QoL					
Baseline	26	2.63	–	–	–
12 weeks	23	1.35	−1.04	−1.54 to −0.55	0.0001
24 weeks	19	1.26	−1.09	−1.76 to −0.41	0.0019
36 weeks	19	1.47	−0.98	−1.87 to −0.10	0.0296
48 weeks	17	1.43	−1.07	−2.16 to 0.02	0.0552
60 weeks	9	1.22	−1.26	−2.56 to 0.05	0.0587
72 weeks	5	1.11	−1.38	−2.94 to 0.19	0.0840
PAC-SYM					
Baseline	26	2.24	–	–	–
12 weeks	23	1.15	−0.97	−1.41 to −0.53	0.0000
24 weeks	18	1.19	−0.92	−1.52 to −0.32	0.0029
36 weeks	19	1.25	−1.03	−1.80 to −0.26	0.0094
48 weeks	17	1.36	−0.97	−1.92 to −0.02	0.0444
60 weeks	9	1.19	−1.16	−2.28 to −0.03	0.0448
72 weeks	5	0.82	−1.51	−2.87 to −0.16	0.0289

All estimates are adjusted for time.

with some quite substantial improvements in measures [e.g. > 25% scalar improvements in psychological measures (e.g. PHQ-9, GAD-7), St Mark's Incontinence Score and EQ-VAS]. Global patient satisfaction was 2.7 points at 24 weeks (nearest to 'very satisfied'), although this dropped to 2.2 points ('moderately satisfied') at 48 weeks. This result was mirrored in the global patient improvement score (EQ-VAS score 0–100 points between 'no effect' and 'complete cure'), which was 72.2 points at 24 weeks and 56.5 points at 48 weeks.

Comparing pre-surgery and post-surgery periods, intervention led to a significant increase in cost (£5012, 95% CI £4446 to £5322), similar to the cost of surgery, and a modest and imprecise increase in QoL (0.043 QALYs, 95% CI −0.005 to 0.093 QALYs). The ICER was £115,512 per QALY. At the NICE threshold of £30,000 per QALY, the probability that surgery is cost-effective within 48 weeks of surgical intervention is 0%. The EVPI (per subject) reflects the opportunity loss of ongoing uncertainty and suggests no requirement for further research.

Laparoscopic ventral mesh rectopexy was shown to be a safe procedure. There were 30 AEs reported by 16 patients, 20 of which were considered to have possible causality related to surgery and none of which had any long-term sequelae. There were five SAEs, of which four were deemed to be related to surgery. Three of these were for postoperative pain, which was entirely to be expected in a proportion of patients; one was for a chest infection and none resulted in long-term patient harm.

Patient experience of lapVMR was, on the whole, positive. Some patients did not find surgery to be the miracle cure that they were looking for and some reported negative experiences in the perioperative period, but for the most part these were not related to the operation itself. Some patients also found benefit from the dietary and behavioural changes that they initiated as a result of advice that they were given as part of the perioperative care package.

The media scrutiny of the use of mesh undoubtedly affected both patient and surgeon perception and willingness to take part in the study. Some centres paused or abandoned lapVMR totally in the light of the mesh scandal, and there was a perception that for others the heightened scrutiny of practice in the protocol also negatively affected recruitment.

Systematic reviews

An aim of the programme was to systematically review outcomes from current surgical approaches to CC, with the aim of integrating new data with old data at the programme conclusion. On this basis, a series of workshops and rounds of Delphi consensus were undertaken, leading to seven major open access publications; these included an introduction and methods paper,[135] five reviews of major procedure classes[136–140] and a summary paper with European graded practice recommendations covering patient selection, benefits and harms of all procedures.[141] These papers have been cited 102 times in the scientific literature and also referenced in major textbooks and the national press; they represent a unique, contemporary and valuable open access resource for clinicians and researchers worldwide. The review of rectopexy confirmed that lapVMR evidence was confined to 18 studies, all of which contained poor-quality (Oxford Centre for Evidence-Based Medicine grade IV) observational data (case series and poor-quality cohort studies); these data provided the rationale for CapaCiTY trial 3.

Conclusions

Taking together the results from clinical effectiveness, cost-effectiveness and patient experience data, the following conclusions may be drawn while accepting the major caveat of under-recruitment:

- Included patients had a high symptom burden and long duration of symptoms that had been refractory to previous treatments, including a minimum of bowel habit training by a specialist practitioner. Patients had been thoroughly investigated and, therefore, could be considered both 'hard to treat' and 'carefully selected' for surgical intervention.

- Our analysis of clinical effectiveness showed a reduced symptom burden and improved disease-specific QoL. The magnitude of the effect of surgery (estimated reduction of 1.09 points in PAC-QoL at 24 weeks) was greater than the minimum clinically important difference sought by design (mean change 1.0 points) and this change was statistically significant. In addition, significant and clinically important improvements in PAC-SYM score and bowel frequency provided further evidence of the benefit of surgery.
- The findings of the primary outcome showed a continued improvement for the duration of the study period (estimated 1.38-point reduction in PAC-QoL at 72 weeks), and this finding was supported by a panel of secondary outcome measures, accepting inferential limitations posed by potential attrition bias.
- Serious under-recruitment limited the scope to conduct economic analysis. To explore the potential cost-effectiveness of lapVMR some assumptions were necessary: (1) the effect of surgery was not affected by allocation (and thus delay to surgery); (2) growth curve analysis is a reliable method to characterise pre-surgery and post-surgery costs and QoL; (3) pre-surgery non-surgery costs and EQ-5D-5L scores are stable, making it possible to construct a single pre-surgery follow-up covering the 48 weeks before surgery; and (4) benefits following surgery are limited to the first 48 weeks following surgery. The weakest of these assumptions might be limiting benefit from surgery to 48 weeks; any future QALY gain and reduced burden from decreased use of the health-care system for symptoms of CC would make surgery more cost-effective. Potential longer-term complications of mesh insertion and removal were not considered, but if emergent would reduce cost-effectiveness.
- The base case suggests that lapVMR is not cost-effective ($p = 0.00$ at a WTP threshold of £30,000 per QALY). However, because this finding comes from an observational analysis of a stepped-wedge design, and for the reasons described, it remains vulnerable to bias that might increase or decrease cost-effectiveness.
- Although some adverse effects were reported, lapVMR was safe and well tolerated overall.
- Some patients described how their bowel function was better immediately after surgery and had continued success, and these patients noted a better QoL both mentally and physically; others found the benefit to be short-lived or did not feel any change. Pain was a significant issue for some patients. The mesh controversy dominated staff experience.

Reflections on work programme 4

The study was severely hampered by under-recruitment. Difficulties in attracting centres to recruit pre-dated the zenith of the mesh scandal and reflected wide variation in practice across the UK in terms of both patient selection and lapVMR operative technique. The mesh scandal undoubtedly compounded the recruitment problems faced by the study and yet paradoxically emphasised the need for such a study to take place. It was, for instance, very clear that the attention we paid to strict inclusion and exclusion criteria [actually based on guidance from the Pelvic Floor Society (London, UK)[134]] led to increased scrutiny in many centres where such surgery was being undertaken without rigorous application of these criteria. This regrettably (for the trial but not the patients concerned) led to a rapid revision (manifest as a drop-off) in the number of patients available at several centres for recruitment. Unfortunately, with the evolution of the media storm against placement of pelvic mesh and worldwide class actions against surgeons and manufacturers of mesh, the issue of patient selection has now made its way to the courts. Therefore, although it might be argued that the study design was overzealous in its approach to inclusion and exclusion, the decision of our expert panel to rigidly maintain the selection and procedural standards laid out in the protocol was undoubtedly the right one.

With the media storm blowing up and the Cumberlege report[142] in preparation, there was never a time when the results of this trial were more needed, and we were very disappointed by our failure to keep the trial going. This was not for want of trying. With the strong support of the Association of Coloproctology of Great Britain and Ireland, the Pelvic Floor Society wrote on our behalf to NHS England seeking its support for a mandate to surgeons in England and Wales to continue surgery only

in the context of research indemnity. This request, if granted, would have helped push recruitment and prevented some hospitals from abandoning the operation, thus denying patients access to lapVMR and the scientific community an answer to the main trial questions.

However, despite these setbacks, the main aim of the trial, namely to determine the effect size of surgery for the first time in a high-quality experimental design, and thus improve on the level IV evidence provided by 18 case series (as outlined in our systematic review),[140] was addressed, albeit at a lower than desirable level of statistical power. Being to our knowledge the only high-quality evidence in the field, our results show substantial symptomatic benefit (more than we sought by design) to a cohort of highly selected patients from lapVMR performed to a standardised technique.

Cost-effectiveness analysis was disappointing and, as with all expensive (surgical) interventions, we did not show a cost benefit in the short term (to 48 weeks). Enthusiasts will say that the benefit of mesh placement is economically apparent only in the long term. It is also difficult to demonstrate cost-effectiveness in our multiply comorbid patients whose overall sense of well-being (as measured by the EQ-5D-5L) is only partially affected by improvement in bowel-associated symptoms.

Research recommendations

The current COVID-19 pandemic has created a natural hiatus in the provision of nearly all non-urgent benign surgery. This has coincided with the publication of the Cumberlege report[142] and together these provide a 'pause for thought' on the future use of lapVMR in patients with CC. Despite the underpowering of our study, it is unlikely that such a trial will be repeated (at least in the UK). Rather, it is likely that enthusiasts will cite the effect size in our study as mirroring that in observational trials, balancing this against the very real risk of harm (notably the small proportion of patients with long-term mesh complications). The reduction in anxiety surrounding the use of mesh as time passes and the production of updated consensus guidance on patient selection and operative technique may make further study in this area feasible.

Work programme 5: synthesis of trial data and conclusions

A stated aim of the programme was to develop an NHS pathway for the management of CC in adults based on data synthesis. Specifically, we stated that 'findings will be assimilated and synthesised with previous research, and a national working group convened to develop a new treatment pathway for management of CC in adults'. To this end each participant had a unique ID so that they could be followed through each of the trials. Considerable under-recruitment, reflecting the difficulties of recruiting the patient population, severely limited the scope for an integrated analysis or pathway. However, with all the caveats noted, evidence from the CapaCiTY trials supports the value of standard-care habit training and high-volume TAI and questions the value of habit-training with biofeedback, INVEST procedures and low-volume TAI. The findings as they pertain to lapVMR are mixed and lend some support to this procedure in a highly defined population with informed consent.

With these conclusions in mind, *Figure 8* provides a revision of the pathway schematic presented in *SYNOPSIS*. Here, patients receive a standardised intervention with habit training, and only if this fails do they progress to INVEST. Thence, selected patients with the specific diagnosis of dyssynergic defaecation can undergo direct visual biofeedback, and others can undergo TAI, this being initiated by default with a high-volume device. Patients progressing to a MDT meeting for consideration of surgery may be offered lapVMR if they meet the strict selection criteria, but the consent process must include realistic data on the immediate and longer-term benefits (or otherwise) of this procedure, noting that enhanced consent procedures with standardised proformas and patient information leaflets (provided by the Pelvic Floor Society) are already best practice in relation to detailing long-term harms. Surgeons could, for instance, cite a conservative interpretation of our data in relation to reduced bowel symptoms but falling overall satisfaction with surgery over time, as well as little or no improvement in general QoL.

Reflections on the whole research programme and overall conclusions

How will the international community receive such a pathway? We feel that the answer to this in the UK is with general positivity. Over the 6 years that the CapaCiTY research programme has run, from initial meetings at national society conferences to the present, we have witnessed hugely positive engagement from experts in the field through to more general audiences. Our ability to bring together the specialist community, both specialists whose centres recruited and specialists whose centres were unable, has proved a major triumph of the programme. Although this is not measurable in adequately powered clinical-effectiveness data, it can be inferred by how many units have standardised their approach to diagnostics and therapy by education through the programme. Furthermore, conclusions from our systematic reviews have already entered major textbooks and have received national and international platforms for presentation. Dissemination activity is ongoing, and there is no doubt that we will be invited for national and international presentation of the conclusions of the three CapaCiTY trials. These 'softer' end points will be the main enduring legacy of the CapaCiTY research programme and the lives of people living with CC will be the better for it.

Lessons learned for future research

The considerable challenges to recruitment for all three trials have been noted. *Table 5* outlines some insights about how these problems might be mitigated in the future.

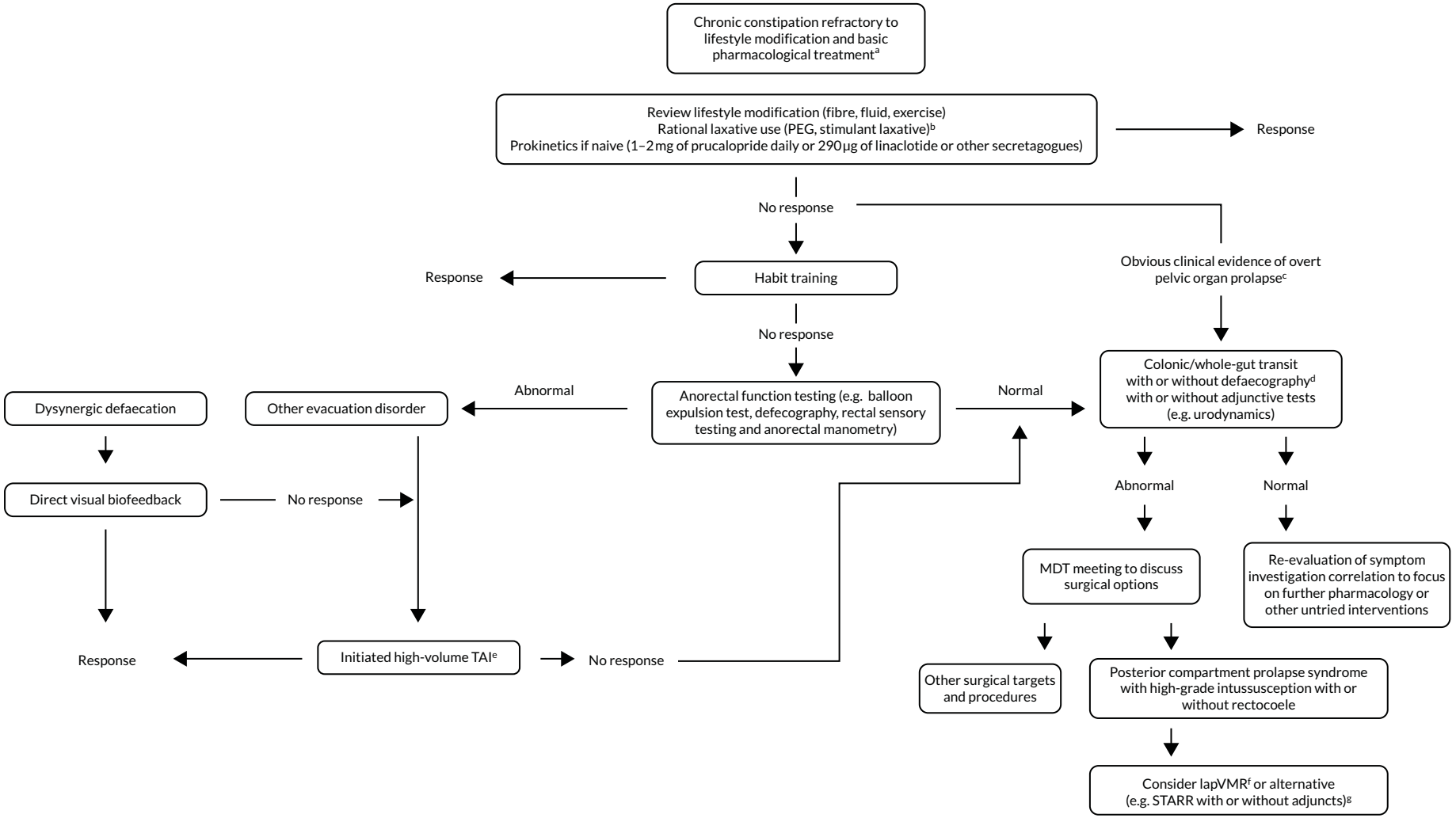

FIGURE 8 Revised prototype pathways of care informed by results of the CapaCiTY research programme. a, Alarm features excluded and secondary causes treated appropriately; b, in IBS-C, consider antispasmodics or neuromodulators in case constipation improves but abdominal pain persists and is dominant symptom; c, examples of overt prolapse include anterior (stage 3 cystocele), middle (stage 3 rectocele, uterovaginal prolapse) and posterior compartments (grade IV/V intussusception); d, if not performed previously; e, unless patient preference is for low-volume TAI or there are specific contraindications to high-volume TAI; f, may reduce specific symptoms but not have overall effect on QoL; g, common adjuncts include sacrocolpopexy, hysterectomy, transvaginal tape and cystocele repair. IBS-C, constipation-predominant irritable bowel syndrome; PEG, polyethylene glycol[0].

TABLE 5 Lessons learned for future research

Problem	Mitigation	Notes
Design: three concurrent RCTs of complex interventions	Limit to one or two major RCTs in a programme recommended Alternative design	Although the team made considerable efforts to support each trial and we had sequential start dates, the dilution of focus and effort was probably a factor, especially with trying to 'market' more than one trial per recruitment centre. Disruption to the original planned sequence occurred because of set-up delays. The three-group design of study 1 was certainly overambitious, with INVEST leading to delays in recruitment to any group. With hindsight, an alternative design that incorporates experimental evaluations in a longitudinal cohort of patients would have been more appropriate, such as a TwiCs design. TwiCs designs have become increasingly popular during the period of the research programme, including pragmatic evaluations of complex interventions such as surgery. A TwiCs design would have provided a much greater cohort of patients with longitudinal observations of symptoms, QoL data and data on the effect of ongoing routine clinical care; this would have proved a valuable source of new learning in its own right
'Fat file' as a deterrent to patients and local investigators	Reduce outcome frequency and number. Adhere to 'one trial, one question'	One problem of clinical programmes is trying to appease everyone's interests, thus trying to rigorously cover aspects of qualitative and quantitative outcomes relevant to specialist clinical, QoL, health economic and psychological outcomes. This enthusiasm must be tempered with the reality of what is possible
Protocol compatibility with routine clinical practice	Increase pragmatism. Avoid or reduce standardisation of complex interventions	We tried (rightly) to answer the 'important questions', but the complexity of these led to the need for standardisation. This constrained clinicians to a point where many did not buy in to the agreed protocol. A better balance of standardisation vs. clinician-decisive care might have improved uptake, particularly in the nursing community
Choice of trial interventions: attribution of costs and NHS resources	Choose NHS interventions that reduce cost and complexity. Think 'what research question can we answer' before 'what do we want to answer'	We would advise future investigators to think very carefully about embarking on a RCT that requires complex interventions over and above routine care. The staffing to deliver complex research interventions in the NHS (even pre COVID-19) is fragile and most of our recruitment came care of directly funded research staff. ETCs make this even less tenable. In our experience, CRNs proved unable to resolve issues when individual trusts viewed research as a low priority compared with clinical delivery. Surgery added the additional problem of waiting-time inflexibility

continued

TABLE 5 Lessons learned for future research (*continued*)

Problem	Mitigation	Notes
Set-up time in multiple centres	Perform pre-trial recruitment feasibility studies rather than relying on site surveys	We grossly underestimated delays in R&D approval processes, with some experienced sites (with a willing principal investigator) taking up to 1 year to open from receiving all study documentation, and this despite intervention by the host CRN on our behalf. Several never opened
Failure of early learning from qualitative data	Perform some interviews (e.g. of staff) early in programme	We did not include a process evaluation in our programme but could have used some of the eventual qualitative analysis from staff and patients to troubleshoot some of the recruitment issues that we encountered

Patient and public involvement

Patient representation in the CapaCiTY research programme supported all research activities. The focus of the CapaCiTY research programme from a PPI perspective was to convene a Constipation Research Advisory Group (CRAG) comprising eight patients and two carers from London, UK, and Durham, UK. This group had geographical diversity (covering both north and south England) and a disease-appropriate demographic (eight female and two male participants). PPI was managed by two co-applicants and the CRAG had an active 'contributory' rather than 'representative' role. The overarching functions of the CRAG included:

- managing the research (e.g. steering/advisory group)
- developing participant information resources
- advising on protocol revisions (in particular on recruitment and participant burden)
- disseminating of research findings.

Although CRAG members had patient knowledge of living with severe CC, they did not have the same knowledge of clinical trial and medical research terminology as the research team. Because CRAG members were invited (in rotation) to sit on the Programme Steering Committee (PSC), this put them at a disadvantage. Therefore, training was provided to CRAG members at the start of the project in 2015 that included taking part in an activity in identifying barriers to recruitment in clinical trials and potential solutions. This enabled the CRAG members to review all patient-facing documents including the patient information sheet, patient diaries and patient journals at the beginning of the programme for all three trials. It also enabled them to feel more comfortable when they attended a PSC meeting.

The CRAG was actively involved and effective in providing lay advice and guidance in areas of trial feasibility, design, management, marketing, analysis, recruitment and reporting. Furthermore, CRAG members reviewed all patient-facing material during the substantial amendment in 2016. The CRAG was also consulted about reducing the length of follow-up from 24 to 12 months.

The CRAG reported and made recommendations to the PSC. It was agreed that normally CRAG meetings would be held every 6 months prior to the PSC (ideally 1 month before). The CRAG would feed recommendations back to the PSC. Therefore, the CRAG had a significant role in strategic decision-making. For example, in 2017 the CRAG was provided with a detailed presentation as per the PSC's recommendation. The PSC asked that the CRAG answer whether or not the CRAG deemed CapaCiTY trial 2 futile owing to under-recruitment. Although it was noted that the inclination of the PSC was to continue, they were keen to consult with the CRAG. The group discussed at length the key areas under consideration, which included the following: was it safe for the patients participating in the trial? Was it cost-effective to continue? Would the research questions be answered?

Though the group accepted that, ideally, more patients should be recruited to improve the accuracy and validity of the data results, it was generally agreed that 100 patients was an acceptable milestone.

The CRAG also discussed financial matters. However, the main focus of the in-depth discussion was whether or not the research questions would be answered. Owing to the smaller sample size it was recognised that the primary research question could be compromised. However, the CRAG recognised the importance of being able to answer many other questions in relation to high-volume and low-volume TAI treatments. The CRAG discussed the value and importance of the secondary data that had been captured to date and data that would continue to be collected if the trial was to continue. It was evident that from a patient perspective these data were of significance. It was noted that the CRAG wished to avoid any negative messaging and in particular did not wish to put off future patients from entering a trial because of the possibility of cancellation.

This consultative approach between the PSC and CRAG, seeking to direct and support the three trials, ensured that both researchers and patients had a mutual understanding of what was required. This ensured that the findings of the three trials would be of benefit to participants in those clinical trials. In addition, three members of the CRAG held a teleconference with Christine Norton and Shiva Taheri to contribute to the interpretation of the interview data and to agree and support the main messages for dissemination.

Overall, patient representation made a major contribution to design, conduct and recruitment of the CapaCiTY research programme. The CRAG was involved in all major decisions that were made during the programme, which meant that patient benefit was always put first in everything we did. The CRAG will continue to support the CapaCiTY research programme in dissemination activities, including at the Bowel Research UK annual Big Bowel Event.

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- Tiffany Wade for interviews and qualitative analysis.

Programme Steering Committee

Ian McCurrach and Louisa Smalley (PPI representatives) and Daniel Altman and Melanie Smuk (programme statisticians).

Data Monitoring Committee

David Jayne (chairperson), Rupert Pearse (independent clinician) and Neil Corrigan (independent statistician).

Contributions of authors

Charles H Knowles (https://orcid.org/0000-0001-9854-6754) (Professor of Surgery) was chief investigator of the CapaCiTY programme

Lesley Booth (https://orcid.org/0000-0001-5812-4549) (Patient and Bowel Research UK Charity Research Director) was lead for PPI.

Steve R Brown (https://orcid.org/0000-0002-0980-2793) (Professor of Colorectal Surgery) was co-principal investigator for CapaCiTY trial 3.

Samantha Cross (https://orcid.org/0000-0002-0501-0289) (Lecturer in Medical Statistics) conducted statistical analyses and summarised results in tables for all three CapaCiTY trials.

Sandra Eldridge (https://orcid.org/0000-0001-5638-2317) (Professor of Statistics) provided senior oversight of trial design and all statistical analyses.

Christopher Emmett (https://orcid.org/0000-0002-6022-8475) (Clinical Research Fellow, Gastroenterology) assisted with recruitment and provided clinical support for CapaCiTY trial 2.

Ugo Grossi (https://orcid.org/0000-0001-5372-2873) (Clinical Research Fellow, Surgery) assisted with recruitment and provided clinical support for CapaCiTY trials 1 and 3.

Mary Jordan (https://orcid.org/0000-0002-0497-8634) (Senior Research Fellow, Health Economics) conducted the analysis of economic models.

Jon Lacy-Colson (https://orcid.org/0000-0002-5151-8358) (Consultant Colorectal Surgeon) was co-principal investigator for CapaCiTY trial 3.

James Mason (https://orcid.org/0000-0001-9210-4082) (Professor of Health Economics) provided senior oversight of health economic analyses and modelling.

John McLaughlin (https://orcid.org/0000-0001-6158-5135) (Professor of Gastroenterology) served as chairperson of the PSC and contributed to the study write up.

Rona Moss-Morris (https://orcid.org/0000-0002-2927-3446) (Professor of Psychology) conducted analyses and write-up of all psychological outcomes.

Christine Norton (https://orcid.org/0000-0003-2259-0948) (Professor of Nursing) was co-principal investigator for CapaCiTY trial 1 and oversaw all qualitative studies.

S Mark Scott (https://orcid.org/0000-0002-7997-1533) (Senior Health Scientist) was co-principal investigator for CapaCiTY trial 1 and oversaw analysis of all INVEST interventions.

Natasha Stevens (https://orcid.org/0000-0002-3910-7863) (Senior Trials Manager) provided programme management for all three trials (during years 1 and 2) and assisted development of the CapaCiTY research programme.

Shiva Taheri (https://orcid.org/0000-0003-0879-0601) (Trials Manager) provided programme management for all three trials (during years 3–5).

Yan Yiannakou (https://orcid.org/0000-0001-8437-2925) (Professor of Gastroenterology) was principal investigator for CapaCiTY trial 2.

Publications

Original research

Etherson KJ, Horrocks EJ, Scott SM, Knowles CH, Yiannakou Y. A national biofeedback practitioners service evaluation: focus on chronic idiopathic constipation. *Frontline Gastroenterol* 2017;**8**:62–7. https://doi.org/10.1136/flgastro-2015-100660

Trial protocols

Emmett C, Close H, Mason J, Taheri S, Stevens N, Eldridge S, *et al.* Low-volume versus high-volume initiated trans-anal irrigation therapy in adults with chronic constipation: study protocol for a randomised controlled trial. *Trials* 2017;**18**:151. https://doi.org/10.1186/s13063-017-1882-y

Norton C, Emmanuel A, Stevens N, Scott SM, Grossi U, Banister S, *et al.* Habit training versus habit training with direct visual biofeedback in adults with chronic constipation: study protocol for a randomised controlled trial. *Trials* 2017;**18**:139. https://doi.org/10.1186/s13063-017-1880-0

Grossi U, Stevens N, McAlees E, Lacy-Colson J, Brown S, Dixon A, *et al.* Stepped-wedge randomised trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation: study protocol for a randomised controlled trial. *Trials* 2018;**19**:90. https://doi.org/10.1186/s13063-018-2456-3

Systematic reviews

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Reports of studies not yet published

CapaCiTY trial 1: habit training compared with habit training with direct visual biofeedback in adults with chronic constipation – randomised controlled trial

Intervention

Habit training was provided by a trained specialist (nurse or physiotherapist with clinical experience) who had undertaken a standard 1-day (study-specific) training session. A standardised approach and intervention were provided using an intervention manual (see *Appendix 2*, *CapaCiTY trial 1: intervention protocols*), and at least one random observation visit was performed early in the study by lead researchers for quality control.

The course of therapy included three or four sessions (with interval tolerance of every 3–5 weeks). The first and last sessions were always face to face. Sessions were delivered by the same therapist if at all possible and tailored to a participant's individual needs.

Habit training with biofeedback included the steps of habit training plus direct visual biofeedback using a portable HRAM manometry catheter connected to a computer monitor. Calibration, validation and maintenance of the equipment were built in to the programme and training manuals were provided. Training on the standardised system and protocol was performed and documented in the investigator site file prior to sites commencing treatment. The outcomes of each session, including the ability to expel the balloon, generate propulsion, increase rectal pressure, relax the anal canal and sense the balloon at lower or higher volumes (relevant to hyposensate and hypersensate patients) over successive sessions were recorded on an intervention CRF.

Trial design features

Basic design

A parallel, three-group, randomised trial design permitted two randomised comparisons: an overall evaluation of the performance of a panel of INVEST in improving the selection of treatment and an evaluation of treatment options (HT vs. HTBF) without INVEST. Thus, the overall evaluation addressed whether or not INVEST-guided care led to more favourable outcomes than randomised allocation.

Sample size calculation

Sample size was calculated using the primary clinical outcome, change in PAC-QoL score. A 10% scale difference or 0.4-point reduction in PAC-QoL score with a variance estimate conservatively set at SD = 1 was considered clinically relevant. To detect a mean change of 0.4 points in PAC-QoL score (SD = 1) with 90% power and 5% significance level, 132 participants per group or 264 participants in total was required for the comparison of HT and HTBF (no-INVEST group).

For the secondary comparison of INVEST and no INVEST, a reduction of 0.4 points (SD = 1) was also considered clinically meaningful. To detect an effect size of 0.4 points with 90% power and 5% significance level required 90 participants in the INVEST group, assuming 264 participants were recruited to the no-INVEST group.

Allowing for 10% loss to follow-up, a sample size of 147 participants was needed in both the HT and HTBF groups and 100 participants in the INVEST group. A total sample size of 394 participants across the three groups was required.

Randomisation procedure

Randomisation (with an allocation ratio of 3 : 3 : 2 to HT, HTBF and INVEST, respectively) occurred at one point in time following recruitment (after eligibility and baseline assessments). Randomisation was stratified by sex (and female participants by centre) with (block size 8) randomisation implemented via an online randomisation system developed by the PCTU. Randomisation was conducted by suitably trained and delegated researchers at recruiting sites and followed PCTU-validated standard operating procedures for the study.

Blinding

Patients and clinicians were necessarily aware of both INVEST and treatment allocations. To minimise bias, where possible, a blinded researcher collected outcome data. If a blinded researcher was not available, the participant completed the questionnaires and placed them in a sealed envelope. Participants were trained in completing questionnaires prior to randomisation and received a visual aid with standardised script and training for completing questionnaires. Quantitative (but not qualitative) outcome assessments were analysed by investigators and statisticians who were blind to allocation status and index intervention.

Concomitant medications

It was inevitable that participants would seek recourse to laxatives and other dietary supplements during the course of the programme. Experience shows that complete prohibition can lead to unreported laxative use, which might confound findings. Although we strongly discouraged ad libitum medication and specified a defined breakthrough regimen, we also recorded (by diary) cotreatment with sufficient fidelity and integrity to enable use as covariates in analyses.

Statistical methods

The primary outcome was analysed on an ITT basis at the 6-month time point. Descriptive statistics (i.e. mean, SD, median and IQR) are presented by trial group. The average reduction in PAC-QoL score was analysed using a linear mixed regression model. The two stratification variables (sex and study site) were included in the model, with site as a random effect and sex as a fixed-effect covariate. Other fixed-effect covariates included in the model were intervention, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).

Secondary outcomes were also analysed on an ITT basis and presented as descriptive statistics by trial group: continuous variables (e.g. PAC-QoL score) were summarised by treatment group (using mean, SD, median and IQR). For categorical variables, numbers and percentages of patients reporting each response option were presented by trial group. Given the much smaller than target number of patients recruited to the trial, it was agreed that adjusted analysis would be performed on secondary outcomes 1 to 3 (i.e. PAC-QoL score) only, with unadjusted treatment differences and 95% CIs for other secondary outcomes. Results obtained using the CC-BRQ and BIPQ-CC have been omitted pending further analysis.

For cost-effectiveness, patients were randomised in parallel trial groups to (1) HT, (2) HTBF or (3) INVEST-recommended treatment using (1) or (2). The three-way cost-effectiveness comparison required the presentation of the cost-effectiveness acceptability frontier (CEAF) in addition to CEACs for each trial group, as the CEAF correctly identifies the optimal decision across the range of WTP thresholds when more than two options are being considered.[143] For this trial, the baseline (0 months) was set after completion of treatment, at the beginning of 12 months of follow-up. Treatment began an average of 3 months before this baseline. Consequently, the duration of follow-up is 15 months, and discounting of costs and QALYs ($r = 0.035$) has been applied to the last 3 months.

Recruitment

Recruitment started on 26 March 2015 (first intervention 21 May 2015) and ended 30 June 2018. A total of 182 patients (target 394 patients) were randomised out of 502 patients screened (36.3%) from 10 sites. Reasons for screen failure are shown in *Figure 9*. Two sites opened but failed to recruit; the remainder randomised

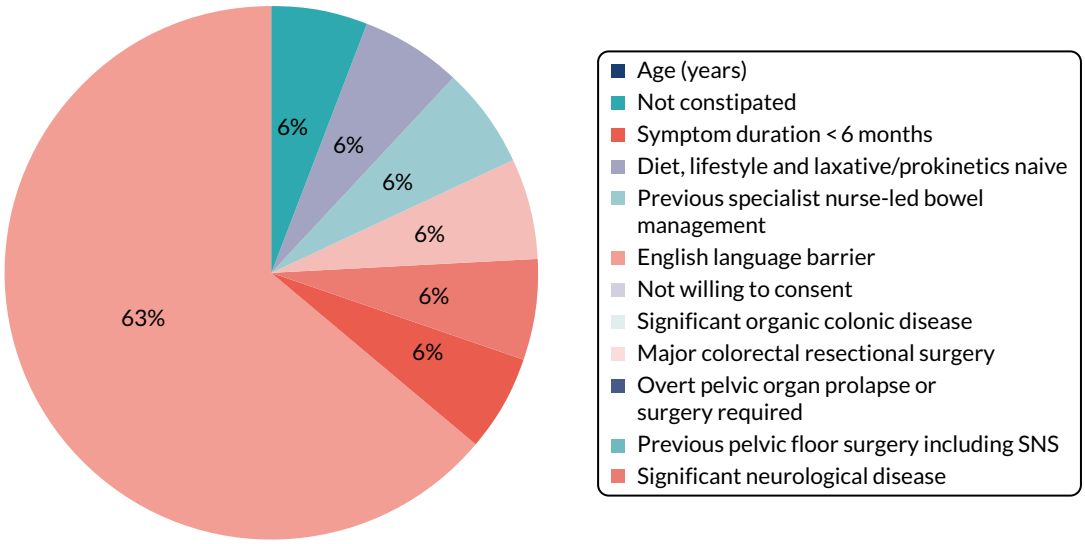

FIGURE 9 The CapaCiTY trial 1 screen failures. SNS, sacral nerve stimulation.

between 7 and 71 patients. A total of 182 patients were randomised: 68 to HT, 68 to HTBF and 46 to INVEST-guided therapy (HT or HTBF based on results). A total of 79 participants dropped out of the study before the primary end point, leaving 103 participants at 6 months. The CONSORT flow diagram is shown in *Figure 2*.

Baseline characteristics

Table 6 shows the numbers and percentages of patients with baseline characteristics presented by trial group. Continuous variables (e.g. age) were summarised by treatment group using mean and SD (and median and IQR if non-normally distributed). *Table 7* shows the data for outcome measures at baseline. These were comparable between three trial groups for all major characteristics.

TABLE 6 Demographic and clinical characteristics of patients randomised

Characteristic	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
Referral method*, n *(%)					
Primary care	18 (26.5)	8 (11.8)	26 (19.1)	11 (23.9)	37 (20.3)
Secondary care	24 (35.3)	32 (47.1)	56 (41.2)	16 (34.8)	72 (39.6)
Tertiary care	14 (20.6)	15 (22.1)	29 (21.3)	10 (21.7)	39 (21.4)
Other	11 (16.2)	12 (17.6)	23 (16.9)	8 (17.4)	31 (17.0)
Missing	1 (1.5)	1 (1.5)	2 (1.5)	1 (2.2)	3 (1.6)
Demographic characteristic					
Sex, *n* (%)					
Male	8 (11.8)	8 (11.8)	16 (11.8)	6 (13.0)	22 (12.1)
Female	60 (88.2)	59 (86.8)	119 (87.5)	39 (84.8)	158 (86.8)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Ethnicity, *n* (%)					
Asian	11 (16.2)	10 (14.7)	21 (15.4)	5 (10.9)	26 (14.3)
Black	7 (10.3)	8 (11.8)	15 (11.0)	5 (10.9)	20 (11.0)
Mixed	1 (1.5)	0 (0.0)	1 (0.7)	2 (4.3)	3 (1.6)

continued

TABLE 6 Demographic and clinical characteristics of patients randomised (*continued*)

Characteristic	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
White	48 (70.6)	49 (72.1)	97 (71.3)	33 (71.7)	130 (71.4)
Other	1 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Age (years)					
Mean (SD)	45.2 (13.6)	45.7 (15.6)	45.4 (14.6)	43.6 (12.2)	45.0 (14.0)
Median (IQR)	47.5 (34.5–57.0)	44.0 (31.0–62.0)	46.0 (33.0–57.0)	42.0 (32.0–53.0)	44.5 (33.0–57.0)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Past medical history*, n *(%)					
Total	50 (73.5)	52 (76.5)	102 (75.0)	35 (76.1)	137 (75.3)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Cardiovascular condition	13 (19.1)	10 (14.7)	23 (16.9)	7 (15.2)	30 (16.5)
Heart disease	1 (1.5)	2 (2.9)	3 (2.2)	0 (0.0)	3 (1.6)
Hypertension	9 (13.2)	6 (8.8)	15 (11.0)	4 (8.7)	19 (10.4)
Hypercholesterolaemia	8 (11.8)	7 (10.3)	15 (11.0)	4 (8.7)	19 (10.4)
Other	3 (4.4)	1 (1.5)	4 (2.9)	2 (4.3)	6 (3.3)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Respiratory condition	15 (22.1)	12 (17.6)	27 (19.9)	9 (19.6)	36 (19.8)
Asthma	13 (19.1)	11 (16.2)	24 (17.6)	9 (19.6)	33 (18.1)
COPD	5 (7.4)	2 (2.9)	7 (5.1)	0 (0.0)	7 (3.8)
Other	2 (2.9)	0 (0.0)	2 (1.5)	0 (0.0)	2 (1.1)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Gastrointestinal condition	23 (33.8)	19 (27.9)	42 (30.9)	20 (43.5)	62 (34.1)
IBS	11 (16.2)	14 (20.6)	25 (18.4)	16 (34.8)	41 (22.5)
Crohn's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ulcerative colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	1 (1.5)	0 (0.0)	1 (0.7)	1 (2.2)	2 (1.1)
Colonic polyps	7 (10.3)	2 (2.9)	9 (6.6)	4 (8.7)	13 (7.1)
Other	8 (11.8)	5 (7.4)	13 (9.6)	5 (10.9)	18 (9.9)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Metabolic condition	9 (13.2)	8 (11.8)	17 (12.5)	7 (15.2)	24 (13.2)
Diabetes	5 (7.4)	1 (1.5)	6 (4.4)	1 (2.2)	7 (3.8)
Hypothyroidism	2 (2.9)	6 (8.8)	8 (5.9)	4 (8.7)	12 (6.6)
Hyperthyroidism	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Other	2 (2.9)	0 (0.0)	2 (1.5)	1 (2.2)	3 (1.6)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Haematological condition	3 (4.4)	4 (5.9)	7 (5.1)	3 (6.5)	10 (5.5)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Hepatic condition	1 (1.5)	1 (1.5)	2 (1.5)	0 (0.0)	2 (1.1)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)

TABLE 6 Demographic and clinical characteristics of patients randomised (*continued*)

Characteristic	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
Renal disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.5)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Genito-urinary condition	10 (14.7)	12 (17.6)	22 (16.2)	4 (8.7)	26 (14.3)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Neurological/CNS condition	14 (20.6)	14 (20.6)	28 (20.6)	6 (13.0)	34 (18.7)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Psychiatric condition	15 (22.1)	10 (14.7)	25 (18.4)	12 (26.1)	37 (20.3)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Dermatological condition	12 (17.6)	11 (16.2)	23 (16.9)	5 (10.9)	28 (15.4)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Musculoskeletal condition	6 (8.8)	12 (17.6)	18 (13.2)	5 (10.9)	23 (12.6)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Other condition	11 (16.2)	16 (23.5)	27 (19.9)	9 (19.6)	36 (19.8)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Past surgical history*, n *(%)					
Total	36 (52.9)	35 (51.5)	71 (52.2)	22 (47.8)	93 (51.1)
Abdominal operation	13 (19.1)	11 (16.2)	24 (17.6)	7 (15.2)	31 (17.0)
Gynaecological procedure	23 (33.8)	24 (35.3)	47 (34.6)	17 (37.0)	64 (35.2)
Proctological or perineal procedure	10 (14.7)	8 (11.8)	18 (13.2)	6 (13.0)	24 (13.2)
Neuromodulation	1 (1.5)	1 (1.5)	2 (1.5)	0 (0.0)	2 (1.1)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Duration (months) of constipation symptoms					
Mean (SD)	72.1 (51.9)	76.8 (56.3)	74.5 (54.0)	75.7 (55.2)	74.8 (54.1)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Previous lifestyle modifications*, n *(%)					
Total	67 (98.5)	67 (98.5)	134 (98.5)	45 (97.8)	179 (98.4)
Diet	67 (98.5)	65 (95.6)	132 (97.1)	44 (95.7)	176 (96.7)
Fluid	62 (91.2)	64 (94.1)	126 (92.6)	41 (89.1)	167 (91.8)
Exercise	54 (79.4)	58 (85.3)	112 (82.4)	39 (84.8)	151 (83.0)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Alternative therapies*, n *(%)					
Total	7 (10.3)	1 (1.5)	8 (5.9)	1 (2.2)	9 (4.9)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Laxatives*, n *(%)					
Total	67 (98.5)	65 (95.6)	132 (97.1)	45 (97.8)	177 (97.3)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Antidiarrhoeals*, n *(%)					
Total	3 (4.4)	4 (5.9)	7 (5.1)	2 (4.3)	9 (4.9)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)

continued

TABLE 6 Demographic and clinical characteristics of patients randomised (*continued*)

Characteristic	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
Prokinetics*, n *(%)					
Total	9 (13.2)	15 (22.1)	24 (17.6)	7 (15.2)	31 (17.0)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Nurse-led bowel management*, n *(%)					
Total	12 (17.6)	11 (16.2)	23 (16.9)	12 (26.1)	35 (19.2)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Family history of bowel disease*, n *(%)					
IBS	15 (22.1)	11 (16.2)	26 (19.1)	10 (21.7)	36 (19.8)
IBD	1 (1.5)	3 (4.4)	4 (2.9)	5 (10.9)	9 (4.9)
Gastrointestinal cancer	3 (4.4)	7 (10.3)	10 (7.4)	4 (8.7)	14 (7.7)
Other	2 (2.9)	5 (7.4)	7 (5.1)	2 (4.3)	9 (4.9)
Missing	1 (1.5)	2 (2.9)	3 (2.2)	2 (4.3)	5 (2.7)
Sexual history (female participants only)*, n *(%)					
Sexually active	43 (71.7)	40 (67.8)	83 (69.7)	29 (74.4)	112 (70.9)
Child-bearing potential	38 (63.3)	32 (54.2)	70 (58.8)	25 (64.1)	95 (60.1)
> 1 year post menopausal	21 (35.0)	24 (40.7)	45 (37.8)	9 (23.1)	54 (34.2)
Surgically sterile	13 (21.7)	13 (22.0)	26 (21.8)	8 (20.5)	34 (21.5)
Contraceptive use (female participants only)*, n *(%)					
Total	25 (41.7)	19 (32.2)	44 (37.0)	18 (46.2)	62 (39.2)
Barrier	10 (16.7)	8 (13.6)	18 (15.1)	6 (15.4)	24 (15.2)
Non-barrier	15 (25.0)	12 (20.3)	27 (22.7)	12 (30.8)	39 (24.7)
Missing	2 (3.3)	4 (6.8)	6 (5.0)	5 (12.8)	11 (7.0)
Past obstetric history (female participants only)					
Total, *n* (%)	38 (63.3)	37 (62.7)	75 (63.0)	27 (69.2)	102 (64.6)
Number of vaginal deliveries, mean (SD)	1.9 (1.4)	1.8 (1.3)	1.8 (1.4)	1.7 (1.3)	1.8 (1.4)
Number of caesareans, mean (SD)	0.2 (0.5)	0.4 (0.6)	0.3 (0.6)	0.4 (0.8)	0.3 (0.6)
Number of forceps/ventouse deliveries, mean (SD)	0.1 (0.3)	0.2 (0.4)	0.2 (0.4)	0.1 (0.6)	0.1 (0.4)
Number of episiotomies, mean (SD)	0.5 (0.8)	0.4 (0.8)	0.4 (0.8)	0.6 (0.7)	0.5 (0.8)
Number of obstetric tears, mean (SD)	0.6 (0.8)	0.5 (0.7)	0.5 (0.8)	0.8 (0.9)	0.6 (0.8)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Faecal incontinence symptoms*, n *(%)					
Total	38 (55.9)	33 (48.5)	71 (52.2)	29 (63.0)	100 (54.9)
Faecal urgency	30 (44.1)	20 (29.4)	50 (36.8)	19 (41.3)	69 (37.9)
Urge faecal incontinence	14 (20.6)	9 (13.2)	23 (16.9)	11 (23.9)	34 (18.7)
Passive faecal incontinence	9 (13.2)	10 (14.7)	19 (14.0)	10 (21.7)	29 (15.9)
Postdefaecation leakage	10 (14.7)	10 (14.7)	20 (14.7)	15 (32.6)	35 (19.2)
Difficulty wiping clean	24 (35.3)	16 (23.5)	40 (29.4)	24 (52.2)	64 (35.2)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)

TABLE 6 Demographic and clinical characteristics of patients randomised (*continued*)

Characteristic	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
Pelvic organ prolapse symptoms*, n *(%)					
Total	13 (19.1)	14 (20.6)	27 (19.9)	14 (30.4)	41 (22.5)
Vaginal bulging	11 (16.2)	14 (20.6)	25 (18.4)	13 (28.3)	38 (20.9)
External rectal prolapse	1 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)
External uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Urinary symptoms*, n *(%)					
Total	26 (38.2)	17 (25.0)	43 (31.6)	16 (34.8)	59 (32.4)
Urinary incontinence	19 (27.9)	7 (10.3)	26 (19.1)	14 (30.4)	40 (22.0)
Urinary urgency	16 (23.5)	13 (19.1)	29 (21.3)	13 (28.3)	42 (23.1)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Joint hypermobility*,[b] n *(%)					
Total	17 (25.0)	15 (22.1)	32 (23.5)	12 (26.1)	44 (24.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CNS, central nervous system; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.
a The HT and HTBF groups together form the no-INVEST group.
b Hypermobility was indicated by a response of 'yes' to two or more out of five questions used to assess joint hypermobility.

TABLE 7 The CapaCiTY trial 1 outcome measures at baseline

Outcome measure	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
PAC-QoL score (points)					
Overall, mean (SD)	2.3 (0.7)	2.4 (0.9)	2.4 (0.8)	2.5 (0.8)	2.4 (0.8)
Missing, *n* (%)	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.3)	4 (2.2)
Dissatisfaction, mean (SD)	3.1 (0.6)	3.2 (0.8)	3.1 (0.7)	3.3 (0.7)	3.2 (0.7)
Missing, *n* (%)	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.3)	4 (2.2)
Physical discomfort, mean (SD)	2.5 (0.8)	2.4 (1.0)	2.4 (0.9)	2.6 (0.8)	2.5 (0.9)
Missing, *n* (%)	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.3)	4 (2.2)
Psychosocial discomfort, mean (SD)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	2.0 (1.0)	1.8 (1.0)
Missing, *n* (%)	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.3)	4 (2.2)
Worries and concerns, mean (SD)	2.3 (1.0)	2.4 (1.0)	2.4 (1.0)	2.6 (0.9)	2.4 (1.0)
Missing, *n* (%)	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.3)	4 (2.2)
PAC-SYM score (points)					
Overall, mean (SD)	2.1 (0.8)	2.0 (0.8)	2.1 (0.8)	2.2 (0.8)	2.1 (0.8)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Stool symptoms, mean (SD)	2.5 (1.0)	2.4 (0.9)	2.4 (0.9)	2.6 (0.9)	2.5 (0.9)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Abdominal symptoms, mean (SD)	2.2 (1.0)	2.0 (1.0)	2.1 (1.0)	2.2 (1.1)	2.1 (1.0)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)

continued

TABLE 7 The CapaCiTY trial 1 outcome measures at baseline (*continued*)

Outcome measure	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST[a] (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
Rectal symptoms, mean (SD)	1.4 (1.1)	1.5 (1.1)	1.5 (1.1)	1.7 (1.2)	1.5 (1.1)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Bowel frequency, number reported over 14 days (diary data)					
Attempts to empty bowels, mean (SD)	26.1 (19.8)	24.9 (16.4)	25.5 (18.1)	26.3 (15.1)	25.7 (17.4)
Missing, *n* (%)	11 (16.2)	14 (20.6)	25 (18.4)	12 (26.1)	37 (20.3)
Times stool was actually passed, mean (SD)	14.8 (10.2)	14.7 (9.9)	14.8 (10.0)	14.3 (8.5)	14.7 (9.7)
Missing, *n* (%)	11 (16.2)	14 (20.6)	25 (18.4)	11 (23.9)	36 (19.8)
Nature of bowel movement, number of days out of 14 (diary data)					
Laxatives used, mean (SD)	4.4 (5.4)	3.3 (5.0)	3.9 (5.2)	5.9 (6.1)	4.3 (5.5)
Missing, *n* (%)	12 (17.6)	14 (20.6)	26 (19.1)	12 (26.1)	38 (20.9)
Glycerine suppositories used, mean (SD)	0.8 (2.6)	0.7 (1.7)	0.7 (2.2)	1.1 (2.8)	0.8 (2.4)
Missing, *n* (%)	12 (17.6)	14 (20.6)	26 (19.1)	13 (28.3)	39 (21.4)
EQ-5D-5L: problems indicated*, n *(%)					
Mobility	16 (23.5)	21 (31.3)	37 (27.4)	11 (25.0)	48 (26.8)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Self-care	8 (11.8)	5 (7.5)	13 (9.6)	6 (13.6)	19 (10.6)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Usual activities	20 (29.4)	24 (36.4)	44 (32.8)	23 (52.3)	67 (37.6)
Missing	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.3)	4 (2.2)
Pain/discomfort	56 (82.4)	55 (82.1)	111 (82.2)	39 (88.6)	150 (83.8)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Anxiety/depression	42 (61.8)	33 (49.3)	75 (55.6)	28 (63.6)	103 (57.5)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
EQ-VAS score (points)					
Total, mean (SD)	67.1 (20.8)	66.6 (18.6)	66.8 (19.7)	61.9 (18.2)	65.6 (19.4)
Missing, *n* (%)	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
PHQ-9 depression severity*, n *(%)					
None	25 (36.8)	26 (38.8)	51 (37.8)	10 (22.7)	61 (34.1)
Mild	22 (32.4)	20 (29.9)	42 (31.1)	17 (38.6)	59 (33.0)
Moderate	11 (16.2)	11 (16.4)	22 (16.3)	11 (25.0)	33 (18.4)
Moderately severe	4 (5.9)	7 (10.4)	11 (8.1)	3 (6.8)	14 (7.8)
Severe	6 (8.8)	3 (4.5)	9 (6.7)	3 (6.8)	12 (6.7)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
GAD-7 anxiety severity*, n *(%)					
None	29 (42.6)	28 (41.8)	57 (42.2)	17 (38.6)	74 (41.3)
Mild	21 (30.9)	16 (23.9)	37 (27.4)	8 (18.2)	45 (25.1)
Moderate	7 (10.3)	13 (19.4)	20 (14.8)	10 (22.7)	30 (16.8)
Severe	11 (16.2)	10 (14.9)	21 (15.6)	9 (20.5)	30 (16.8)
Missing	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)

a The HT and HTBF groups together form the no-INVEST group.

Results: clinical effectiveness

Primary outcome

Table 8 shows the results for the primary outcome.

Secondary outcomes

Table 9 shows changes in PAC-QoL score analysed as binary variables (adjusted analyses) and *Table 10* shows data for individual PAC-QoL domains. All other secondary outcomes are shown in *Tables 11* and *12*. *Figure 10* provides a summary of the similar decrease in PAC-QoL score in all intervention groups.

Supplementary analyses for secondary outcomes included:

1. Binary responses (i.e. responder vs. non-responder) to treatment defined as a ≥ 0.4-point reduction in PAC-QoL score (at 3, 6 and 12 months post end of treatment). A logistic regression model was fitted using the 'xtmelogit' (with logit link) command in Stata. Two stratification variables (sex and study site) are included in the model; sex was included as a fixed-effect covariate in the regression model and site as a random effect. Other covariates in the model were fixed effects for intervention, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).
2. Binary responses to treatment defined as a ≥ 1.0-point reduction in PAC-QoL score (at 3, 6 and 12 months post end of treatment). A logistic regression model was fitted in Stata using the 'xtmelogit' (with logit link) command. Two stratification variables (sex and study site) were included in the model; sex was included as a fixed-effect covariate in the regression model and site as random effect. Other covariates included the model were fixed effects for intervention, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).

Subgroup analyses

Planned subgroup analyses showed no difference in response (e.g. reduction in PAC-QoL score) between patients with or without depression (baseline PHQ-9 score ≥ 5 points), anxiety (baseline GAD-7 score ≥ 4.5 points) or joint hypermobility (baseline joint hypermobility syndrome score ≥ 2 points). However, there was a significant interaction between depression and the INVEST treatment and anxiety and the INVEST treatment.

Safety analyses

The study (not being of a medicinal product) did not record unrelated AEs. Serious adverse events (SAEs) and related AEs were small in number, with only two (both unrelated) SAEs reported (*Table 13*).

TABLE 8 Mean PAC-QoL score by randomised group at 6 months and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in the final analysis model

Intervention	Mean score (points)		Treatment difference[a] (95% CI)	*p*-value
	Baseline (SD)	6 months (SD)		
HT vs. HTBF				
HT ($n = 38$)	2.26 (0.69)	1.49 (0.85)	Reference	
HTBF ($n = 30$)	2.41 (0.81)	1.65 (1.03)	−0.03 (−0.33 to 0.27)	0.8445
No INVEST vs. INVEST				
No INVEST ($n = 68$)	2.33 (0.74)	1.56 (0.93)	Reference	
INVEST ($n = 22$)	2.36 (0.78)	1.81 (1.03)	0.22 (−0.11 to 0.55)	0.1871

a Adjusted for sex, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).

TABLE 9 Binary PAC-QoL score at 3, 6 and 12 months by randomised group and ORs for HT and HTBF and no-INVEST and INVEST groups for those included in the final analysis model

Intervention	PAC-QoL score (points), mean (SD)		Patients with ≥ 0.4-point reduction, *n* (%)	OR for ≥ 0.4-point reduction[a] (95% CI)	Patients with ≥ 1.0-point reduction, *n* (%)	OR for ≥ 1.0-point reduction[a] (95% CI)
	Baseline	Follow-up				
3 months						
HT (*N* = 43)	2.3 (0.7)	1.7 (0.8)	26 (60.5)	Reference	15 (34.9)	Reference
HTBF (*N* = 34)	2.3 (0.9)	1.7 (1.0)	18 (52.9)	0.74 (0.3 to 1.9)	11 (32.4)	0.94 (0.3 to 2.7)
No INVEST (*N* = 77)	2.3 (0.8)	1.7 (0.9)	44 (57.1)	Reference	15 (34.9)	Reference
INVEST (*N* = 26)	2.5 (0.8)	1.9 (1.0)	15 (57.7)	0.95 (0.4 to 2.4)	11 (32.4)	0.34 (0.1 to 1.1)
6 months						
HT (*N* = 38)	2.3 (0.7)	1.5 (0.8)	26 (68.4)	Reference	14 (36.8)	Reference
HTBF (*N* = 30)	2.4 (0.8)	1.7 (1.0)	21 (70.0)	1.09 (0.4 to 3.2)	10 (33.3)	0.91 (0.3 to 2.8)
No INVEST (*N* = 68)	2.3 (0.7)	1.6 (0.9)	47 (69.1)	Reference	14 (36.8)	Reference
INVEST (*N* = 22)	2.4 (0.8)	1.8 (1.0)	12 (54.5)	0.48 (0.2 to 1.4)	10 (33.3)	0.66 (0.2 to 1.9)
12 months						
HT (*N* = 29)	2.2 (0.7)	1.5 (0.8)	16 (55.2)	Reference	9 (31.0)	Reference
HTBF (*N* = 23)	2.2 (0.9)	1.4 (1.2)	16 (69.6)	1.68 (0.5 to 5.6)	7 (30.4)	0.84 (0.2 to 3.0)
No INVEST (*N* = 52)	2.2 (0.8)	1.4 (1.0)	32 (61.5)	Reference	9 (31.0)	Reference
INVEST (*N* = 13)	2.4 (0.8)	1.7 (0.9)	9 (69.2)	1.60 (0.4 to 6.3)	7 (30.4)	1.37 (0.3 to 6.5)

OR, odds ratio.
a Odds ratio comparing HTBF to HT or INVEST to No-INVEST, adjusted for sex, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).

Results: cost-effectiveness

Summary and completeness of data

Participants were allocated randomly to HT, HTBF or INVEST-guided treatment. The average duration of training and support visits for HTBF was greater than for HT, as expected, with the INVEST group falling between these two, reflecting the split allocation. Patients allocated to HTBF completed an average of 2.1 biofeedback training sessions; 43 (93%) patients allocated to INVEST completed the INVEST procedure. The cost of intervention procedures was the predominant determinant of overall cost (*Table 14*) and the only variable differing significantly between groups [one-way analysis of variance (ANOVA), $p < 0.001$]. Use of prescription drugs and community health-care was relatively low and similar between groups. Hence, cost differences were driven by the intervention costs. Societal costs reflected a minority of patients (≈ 20%) reporting substantial time away from work. Completeness of cost data diminished as follow-up progressed from 86% in the first period to 36% in the last period. Quality-of-life scores at each follow-up point and summary QALYs were similar between groups. Similarly, completeness of EQ-5D-5L data diminished as follow-up proceeded from 98% to 35%. An apparent trend of improving quality-of-life in all groups may be confounded by increasing missingness of data.

TABLE 10 Overall PAC-QoL score for individual domains at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in each analysis model at the relevant time point

	3 months				6 months				12 months			
Intervention	*n*	Baseline, mean (SD)[a]	Follow-up, mean (SD)	Treatment difference[b] (95% CI)	*n*	Baseline, mean (SD)[a]	Follow-up, mean (SD)	Treatment difference[b] (95% CI)	*n*	Baseline, mean (SD)[a]	Follow-up, mean (SD)	Treatment difference[b] (95% CI)
Overall score (points)												
HT	43	2.3 (0.1)	1.7 (0.1)	Reference	38	2.3 (0.1)	1.5 (0.1)	Reference	29	2.2 (0.1)	1.5 (0.1)	Reference
HTBF	34	2.3 (0.2)	1.7 (0.1)	−0.02 (−0.3 to 0.3)	30	2.4 (0.1)	1.7 (0.1)	−0.03 (−0.3 to 0.3)	23	2.2 (0.2)	1.4 (0.2)	−0.01 (−0.4 to 0.4)
No INVEST	77	2.3 (0.1)	1.7 (0.1)	Reference	68	2.3 (0.1)	1.6 (0.1)	Reference	52	2.2 (0.1)	1.4 (0.1)	Reference
INVEST	26	2.5 (0.2)	1.9 (0.1)	0.09 (−0.2 to 0.4)	22	2.4 (0.2)	1.8 (0.1)	0.22 (−0.1 to 0.5)	13	2.4 (0.2)	1.7 (0.2)	−0.02 (−0.4 to 0.4)
Dissatisfaction score (points)												
HT	43	3.1 (0.1)	2.1 (0.1)	Reference	38	3.1 (0.1)	2.2 (0.0)	Reference	29	3.1 (0.1)	2.2 (0.0)	Reference
HTBF	34	3.1 (0.1)	2.2 (0.1)	0.17 (−0.3 to 0.6)	30	3.3 (0.1)	2.3 (0.1)	−0.04 (−0.5 to 0.4)	22	3.2 (0.1)	2.0 (0.1)	−0.17 (−0.7 to 0.3)
No INVEST	77	3.1 (0.1)	2.2 (0.0)	Reference	68	3.2 (0.1)	2.2 (0.1)	Reference	51	3.2 (0.1)	2.1 (0.1)	Reference
INVEST	26	3.4 (0.1)	2.4 (0.1)	0.09 (−0.3 to 0.5)	22	3.3 (0.1)	2.3 (0.1)	0.04 (−0.4 to 0.5)	13	3.2 (0.2)	2.0 (0.2)	−0.31 (−0.9 to 0.2)
Physical discomfort score (points)												
HT	43	2.5 (0.1)	1.8 (0.1)	Reference	38	2.5 (0.1)	1.7 (0.1)	Reference	29	2.4 (0.1)	1.6 (0.1)	Reference
HTBF	34	2.3 (0.2)	1.8 (0.2)	0.10 (−0.3 to 0.5)	30	2.4 (0.2)	1.7 (0.2)	0.06 (−0.3 to 0.5)	23	2.2 (0.2)	1.5 (0.2)	0.14 (−0.4 to 0.7)
No INVEST	77	2.4 (0.1)	1.8 (0.1)	Reference	68	2.5 (0.1)	1.7 (0.1)	Reference	52	2.3 (0.1)	1.6 (0.1)	Reference
INVEST	26	2.5 (0.2)	2.1 (0.1)	0.14 (−0.2 to 0.5)	22	2.4 (0.2)	1.9 (0.2)	0.27 (−0.1 to 0.7)	13	2.3 (0.3)	1.8 (0.2)	0.10 (−0.4 to 0.6)

continued

TABLE 10 Overall PAC-QoL score for individual domains at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in each analysis model at the relevant time point (*continued*)

	3 months				6 months				12 months			
Intervention	*n*	Baseline, mean (SD)[a]	Follow-up, mean (SD)	Treatment difference[b] (95% CI)	*n*	Baseline, mean (SD)[a]	Follow-up, mean (SD)	Treatment difference[b] (95% CI)	*n*	Baseline, mean (SD)[a]	Follow-up, mean (SD)	Treatment difference[b] (95% CI)
Psychosocial discomfort score (points)												
HT	43	1.8 (0.1)	1.3 (0.1)	Reference	38	1.7 (0.2)	1.1 (0.1)	Reference	29	1.5 (0.2)	1.1 (0.1)	Reference
HTBF	34	1.8 (0.2)	1.3 (0.2)	−0.05 (−0.4 to 0.3)	30	1.9 (0.2)	1.4 (0.1)	0.07 (−0.3 to 0.4)	23	1.8 (0.2)	1.1 (0.2)	−0.17 (−0.6 to 0.2)
No INVEST	77	1.8 (0.1)	1.3 (0.1)	Reference	68	1.8 (0.1)	1.2 (0.1)	Reference	52	1.6 (0.1)	1.1 (0.1)	Reference
INVEST	26	1.9 (0.2)	1.6 (0.2)	0.21 (−0.1 to 0.6)	22	1.7 (0.2)	1.4 (0.2)	0.24 (−0.1 to 0.6)	13	1.9 (0.3)	1.3 (0.3)	0.02 (−0.4 to 0.5)
Worries and concerns score (points)												
HT	43	2.3 (0.1)	1.7 (0.1)	Reference	38	2.2 (0.2)	1.4 (0.1)	Reference	29	2.3 (0.2)	1.3 (0.1)	Reference
HTBF	34	2.3 (0.2)	1.6 (0.1)	−0.08 (−0.4 to 0.3)	30	2.4 (0.2)	1.6 (0.2)	−0.01 (−0.4 to 0.4)	23	2.2 (0.2)	1.4 (0.2)	0.15 (−0.3 to 0.6)
No INVEST	77	2.3 (0.1)	1.7 (0.1)	Reference	68	2.3 (0.1)	1.5 (0.1)	Reference	52	2.2 (0.1)	1.4 (0.1)	Reference
INVEST	26	2.5 (0.2)	2.0 (0.2)	0.08 (−0.3 to 0.4)	22	2.4 (0.2)	1.9 (0.2)	0.33 (−0.1 to 0.7)	13	2.4 (0.3)	1.7 (0.2)	0.12 (−0.4 to 0.6)

a Observed baseline PAC-QoL score (mean and SD) for those with data at both baseline and follow-up time point. (Statistics only for those included in model.)
b Adjusted for sex, baseline PAC-QoL score and breakthrough medication (i.e. use of oral and/or rectal laxatives).

Note
The results under each time point summarise only the data from participants with recorded outcomes at both baseline and that follow-up time point.

TABLE 11 Other continuous secondary outcomes at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in each of the final analysis models at the relevant time point

	3 months				6 months				12 months			
Continuous outcome	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Treatment difference (95% CI)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Treatment difference (95% CI)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Treatment difference (95% CI)
PAC-SYM score (points)												
Overall												
HT	43	2.2 (0.8)	1.6 (0.8)	Reference	38	2.2 (0.8)	1.5 (0.8)	Reference	29	2.0 (0.8)	1.3 (0.7)	Reference
HTBF	34	2.1 (0.9)	1.7 (1.1)	−0.1 (−0.5 to 0.3)	30	2.1 (0.8)	1.5 (1.1)	−0.1 (−0.5 to 0.3)	23	2.1 (0.9)	1.3 (1.1)	0.0 (−0.5 to 0.5)
No INVEST	77	2.2 (0.8)	1.6 (0.9)	Reference	68	2.1 (0.8)	1.5 (0.9)	Reference	52	2.1 (0.8)	1.3 (0.9)	Reference
INVEST	26	2.3 (0.9)	1.7 (0.9)	−0.1 (−0.5 to 0.3)	22	2.2 (0.9)	1.7 (0.8)	−0.2 (−0.6 to 0.2)	13	2.0 (0.9)	1.4 (0.8)	−0.1 (−0.6 to 0.4)
Stool symptoms												
HT	43	2.6 (0.9)	1.8 (0.9)	Reference	38	2.5 (0.9)	1.8 (1.0)	Reference	29	2.5 (0.7)	1.5 (0.7)	Reference
HTBF	34	2.5 (0.8)	1.8 (1.2)	−0.0 (−0.5 to 0.5)	30	2.5 (0.9)	1.7 (1.3)	0.1 (−0.4 to 0.6)	23	2.5 (0.9)	1.4 (1.2)	0.1 (−0.4 to 0.6)
No INVEST	77	2.6 (0.9)	1.8 (1.0)	Reference	68	2.5 (0.9)	1.8 (1.1)	Reference	52	2.5 (0.8)	1.5 (0.9)	Reference
INVEST	26	2.7 (1.0)	2.0 (1.1)	−0.2 (−0.7 to 0.3)	22	2.6 (1.0)	2.0 (1.0)	−0.3 (−0.8 to 0.2)	13	2.4 (1.2)	1.6 (0.8)	−0.1 (−0.7 to 0.5)
Abdominal symptoms												
HT	43	2.2 (1.0)	1.6 (1.1)	Reference	38	2.2 (0.9)	1.3 (0.9)	Reference	29	2.0 (1.0)	1.4 (1.0)	Reference
HTBF	34	2.0 (1.1)	1.7 (1.1)	−0.1 (−0.6 to 0.4)	30	2.0 (1.0)	1.5 (1.2)	−0.2 (−0.7 to 0.3)	23	1.9 (1.1)	1.3 (1.3)	0.1 (−0.6 to 0.8)
No INVEST	77	2.1 (1.0)	1.6 (1.1)	Reference	68	2.1 (1.0)	1.4 (1.0)	Reference	52	2.0 (1.0)	1.4 (1.1)	Reference
INVEST	26	2.2 (1.0)	1.9 (1.0)	−0.2 (−0.7 to 0.3)	22	2.0 (1.1)	1.7 (1.0)	−0.3 (−0.8 to 0.2)	13	1.7 (0.9)	1.3 (1.0)	0.0 (−0.7 to 0.7)
Rectal symptoms												
HT	42	1.5 (1.1)	1.2 (0.9)	Reference	37	1.5 (1.1)	1.0 (0.8)	Reference	29	1.3 (1.0)	0.7 (0.7)	Reference
HTBF	34	1.6 (1.2)	1.3 (1.3)	−0.1 (−0.6 to 0.4)	30	1.6 (1.1)	1.2 (1.2)	−0.2 (−0.7 to 0.3)	23	1.5 (1.1)	0.9 (1.0)	−0.1 (−0.6 to 0.4)
No INVEST	76	1.5 (1.2)	1.2 (1.1)	Reference	67	1.5 (1.1)	1.1 (1.0)	Reference	52	1.4 (1.0)	0.8 (0.8)	Reference
INVEST	26	1.8 (1.2)	1.2 (1.0)	0.0 (−0.5 to 0.5)	22	1.7 (1.3)	1.1 (0.9)	0.0 (−0.5 to 0.5)	13	1.7 (1.1)	1.1 (1.0)	−0.3 (−0.8 to 0.2)

continued

TABLE 11 Other continuous secondary outcomes at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in each of the final analysis models at the relevant time point (*continued*)

	3 months				6 months				12 months			
Continuous outcome	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Treatment difference (95% CI)**	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Treatment difference (95% CI)**	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Treatment difference (95% CI)**
Diary data												
Bowel frequency: mean number of attempts to empty bowels over 2 weeks												
HT	42	27.9 (22.4)	22.4 (11.9)	Reference	34	29.0 (24.1)	21.8 (11.0)	Reference	25	31.6 (26.1)	24.2 (12.7)	Reference
HTBF	33	23.4 (12.6)	21.7 (12.9)	0.7 (−5.0 to 6.4)	29	26.6 (18.1)	22.6 (13.8)	−0.7 (−7.0 to 5.6)	22	27.4 (19.7)	24.5 (15.0)	−0.3 (−8.4 to 7.8)
No INVEST	75	25.9 (18.7)	22.1 (12.3)	Reference	63	27.9 (21.4)	22.2 (12.3)	Reference	47	29.6 (23.2)	24.4 (13.7)	Reference
INVEST	26	29.9 (15.0)	26.3 (13.6)	−4.2 (−9.9 to 1.5)	22	28.4 (15.6)	23.0 (11.5)	−0.8 (−6.8 to 5.2)	12	24.4 (12.4)	23.0 (11.2)	1.4 (−7.2 to 10.0)
Bowel frequency: mean number of times stool was passed over 2 weeks												
HT	42	15.1 (10.9)	15.9 (10.8)	Reference	34	15.8 (11.7)	14.2 (8.3)	Reference	25	16.2 (11.9)	17.6 (11.1)	Reference
HTBF	33	14.8 (7.6)	16.5 (10.8)	−0.6 (−5.6 to 4.4)	28	14.8 (8.9)	15.4 (11.3)	−1.2 (−6.2 to 3.8)	22	16.2 (9.1)	18.6 (13.0)	−1.0 (−8.1 to 6.1)
No INVEST	75	14.9 (9.5)	16.1 (10.7)	Reference	62	15.3 (10.4)	14.8 (9.7)	Reference	47	16.2 (10.6)	18.1 (11.9)	Reference
INVEST	26	15.0 (9.7)	16.7 (10.9)	−0.5 (−5.4 to 4.4)	22	13.8 (7.7)	14.3 (8.2)	0.5 (−4.1 to 5.1)	12	15.2 (11.4)	17.0 (10.7)	1.1 (−6.4 to 8.6)
Nature of bowel movement: mean number of days (out of 14) laxatives used												
HT	42	4.3 (5.2)	1.0 (3.0)	Reference	34	3.6 (4.5)	0.5 (1.6)	Reference	25	3.8 (4.9)	1.3 (2.5)	Reference
HTBF	33	3.6 (5.0)	1.0 (3.1)	−0.0 (−1.4 to 1.4)	29	3.5 (4.8)	1.0 (2.7)	−0.4 (−1.5 to 0.7)	22	3.6 (5.0)	0.9 (2.2)	0.4 (−1.0 to 1.8)
No INVEST	75	4.0 (5.1)	1.0 (3.0)	Reference	63	3.5 (4.6)	0.7 (2.2)	Reference	47	3.7 (4.9)	1.1 (2.3)	Reference
INVEST	26	6.2 (6.0)	1.7 (4.1)	−0.6 (−2.1 to 0.9)	22	6.2 (6.1)	0.6 (3.0)	0.1 (−1.1 to 1.3)	12	5.1 (5.9)	2.6 (5.4)	−1.5 (−3.5 to 0.5)
Nature of bowel movement: mean number of days (out of 14) glycerine suppositories used												
HT	42	0.8 (2.5)	1.1 (2.3)	Reference	34	0.2 (0.7)	0.8 (2.0)	Reference	25	0.1 (0.3)	0.5 (1.1)	Reference
HTBF	32	0.5 (1.5)	0.9 (2.3)	0.2 (−0.9 to 1.3)	29	0.9 (2.1)	1.2 (2.8)	−0.4 (−1.6 to 0.8)	22	0.6 (1.9)	0.1 (0.3)	0.4 (−0.1 to 0.9)
No INVEST	74	0.7 (2.1)	1.0 (2.3)	Reference	63	0.5 (1.5)	1.0 (2.4)	Reference	47	0.4 (1.3)	0.3 (0.9)	Reference
INVEST	26	1.2 (3.3)	0.8 (2.0)	0.2 (−0.8 to 1.2)	22	1.3 (3.6)	1.2 (3.1)	−0.3 (−1.6 to 1.0)	12	1.3 (4.2)	2.2 (4.0)	−1.8 (−3.0,−0.6)

TABLE 11 Other continuous secondary outcomes at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in each of the final analysis models at the relevant time point (*continued*)

	3 months				6 months				12 months			
Continuous outcome	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Treatment difference (95% CI)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Treatment difference (95% CI)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Treatment difference (95% CI)
EQ-VAS score (points)												
HT	43	68.4 (21.0)	71.0 (21.6)	Reference	39	69.9 (19.7)	69.0 (23.8)	Reference	29	69.7 (18.1)	73.8 (20.2)	Reference
HTBF	34	66.7 (20.1)	71.2 (21.1)	−0.2 (−10.0 to 9.6)	29	66.1 (20.1)	71.0 (20.1)	−2.0 (−12.9 to 8.9)	23	68.8 (17.4)	74.7 (18.8)	−0.9 (−11.9 to 10.1)
No INVEST	77	67.6 (20.5)	71.1 (21.2)	Reference	68	68.3 (19.8)	69.8 (22.1)	Reference	52	69.3 (17.6)	74.2 (19.4)	Reference
INVEST	26	65.3 (17.4)	66.8 (17.6)	4.3 (−4.9 to 13.5)	22	68.1 (16.6)	71.1 (17.3)	−1.3 (−11.6 to 9.0)	13	71.5 (17.4)	71.2 (19.9)	3.0 (−9.1 to 15.1)
PHQ-9 score (points)												
HT	43	8.4 (7.0)	7.8 (7.1)	Reference	38	7.5 (6.5)	7.7 (7.4)	Reference	29	6.7 (6.8)	7.2 (6.5)	Reference
HTBF	34	6.8 (6.4)	6.4 (6.2)	1.4 (−1.7 to 4.5)	30	6.8 (6.4)	7.2 (6.9)	0.5 (−3.0 to 4.0)	23	6.4 (6.8)	5.9 (7.6)	1.3 (−2.6 to 5.2)
No INVEST	77	7.7 (6.8)	7.2 (6.7)	Reference	68	7.2 (6.4)	7.5 (7.1)	Reference	52	6.6 (6.8)	6.6 (6.9)	Reference
INVEST	26	10.0 (6.0)	9.5 (7.4)	−2.3 (−5.4 to 0.8)	22	8.8 (4.8)	8.8 (5.6)	−1.4 (−4.7 to 1.9)	13	8.2 (7.0)	8.2 (7.1)	−1.6 (−5.9 to 2.7)
GAD-7 score (points)												
HT	43	7.4 (6.8)	7.1 (6.9)	Reference	38	6.9 (6.4)	5.8 (6.3)	Reference	29	6.4 (6.4)	6.5 (6.5)	Reference
HTBF	34	7.6 (6.5)	6.6 (6.1)	0.6 (−2.4 to 3.6)	30	7.0 (6.4)	6.4 (6.0)	−0.6 (−3.6 to 2.4)	23	6.2 (6.0)	5.1 (6.3)	1.4 (−2.2 to 5.0)
No INVEST	77	7.5 (6.6)	6.9 (6.5)	Reference	68	7.0 (6.4)	6.1 (6.1)	Reference	52	6.3 (6.2)	5.9 (6.4)	Reference
INVEST	26	8.8 (6.5)	9.2 (6.5)	−2.3 (−5.2 to 0.6)	22	8.4 (6.0)	8.7 (6.4)	−2.6 (−5.6 to 0.4)	13	6.8 (6.1)	7.4 (7.1)	−1.5 (−5.6 to 2.6)
Global patient satisfaction score (points)												
HT	42	–	2.5 (1.0)	Reference	37	–	2.8 (0.9)	Reference	29	–	2.7 (0.8)	Reference
HTBF	32	–	2.4 (1.1)	0.1 (−0.4 to 0.6)	29	–	2.3 (1.3)	0.4 (−0.1 to 0.9)	23	–	2.5 (1.5)	0.2 (−0.5 to 0.9)
No INVEST	74	–	2.5 (1.0)	Reference	66	–	2.6 (1.1)	Reference	52	–	2.6 (1.2)	Reference
INVEST	25	–	2.3 (1.4)	0.2 (−0.3 to 0.7)	21	–	2.5 (1.1)	0.1 (−0.4 to 0.6)	13	–	2.6 (1.1)	−0.0 (−0.7 to 0.7)

continued

TABLE 11 Other continuous secondary outcomes at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and between no-INVEST and INVEST groups for those included in each of the final analysis models at the relevant time point (*continued*)

	3 months				6 months				12 months			
Continuous outcome	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Treatment difference (95% CI)**	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Treatment difference (95% CI)**	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Treatment difference (95% CI)**
Global patient improvement score (points)												
HT	43	–	61.5 (27.8)	Reference	38	–	65.8 (23.1)	Reference	29	–	69.8 (23.2)	Reference
HTBF	34	–	44.9 (34.3)	16.7 (2.6 to 30.8)	28	–	52.7 (35.2)	13.0 (–1.4 to 27.4)	23	–	59.8 (38.0)	10.0 (–7.2 to 27.2)
No INVEST	77	–	54.2 (31.7)	Reference	66	–	60.2 (29.4)	Reference	52	–	65.4 (30.7)	Reference
INVEST	26	–	45.0 (30.8)	9.2 (–5.0 to 23.4)	22	–	45.7 (30.2)	14.5 (0.0 to 29.0)	13	–	62.2 (32.3)	3.2 (–16.0 to 22.4)

Note
The results under each time point summarise only the data from participants with recorded outcomes at both baseline and that follow-up time point.

TABLE 12 Binary secondary outcomes (EQ-5D-5L) at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and no-INVEST and INVEST groups for those included in each of the final analysis models at the relevant time point

	3 months				6 months				12 months		
Binary outcome	***N***	**Indicating problems at baseline, *n* (%)**	**Indicating problems at follow-up, *n* (%)**	**Difference in proportions (95% CI)**	***N***	**Indicating problems at baseline, *n* (%)**	**Indicating problems at follow-up, *n* (%)**	**Difference in proportions (95% CI)**	***N***	**Indicating problems at baseline, *n* (%)**	**Indicating problems at follow-up, *n* (%)**	**Difference in proportions (95% CI)**
Mobility												
HT	43	14 (32.6)	12 (27.9)	Reference	38	11 (28.9)	12 (31.6)	Reference	29	7 (24.1)	5 (17.2)	Reference
HTBF	34	9 (26.5)	12 (35.3)	−0.1 (−0.3 to 0.1)	30	9 (30.0)	12 (40.0)	−0.1 (−0.3 to 0.1)	23	6 (26.1)	8 (34.8)	−0.2 (−0.4 to 0.1)
No INVEST	77	23 (29.9)	24 (31.2)	Reference	68	20 (29.4)	24 (35.3)	Reference	52	13 (25.0)	13 (25.0)	Reference
INVEST	26	9 (34.6)	8 (30.8)	0.0 (−0.2 to 0.2)	22	8 (36.4)	7 (31.8)	0.0 (−0.2 to 0.3)	13	5 (38.5)	4 (30.8)	−0.1 (−0.3 to 0.2)
Self-care												
HT	43	8 (18.6)	8 (18.6)	Reference	38	4 (10.5)	4 (10.5)	Reference	29	2 (6.9)	4 (13.8)	Reference
HTBF	34	4 (11.8)	7 (20.6)	−0.0 (−0.2 to 0.2)	29	4 (13.8)	5 (17.2)	−0.1 (−0.2 to 0.1)	23	4 (17.4)	3 (13.0)	0.0 (−0.2 to 0.2)
No INVEST	77	12 (15.6)	15 (19.5)	Reference	67	8 (11.9)	9 (13.4)	Reference	52	6 (11.5)	7 (13.5)	Reference
INVEST	26	5 (19.2)	4 (15.4)	0.0 (−0.1 to 0.2)	22	4 (18.2)	3 (13.6)	−0.0 (−0.2 to 0.2)	13	1 (7.7)	0 (0.0)	0.1 (0.0 to 0.2)
Usual activities												
HT	43	14 (32.6)	20 (46.5)	Reference	38	10 (26.3)	15 (39.5)	Reference	29	6 (20.7)	8 (27.6)	Reference
HTBF	34	14 (41.2)	15 (44.1)	0.0 (−0.2 to 0.2)	30	13 (43.3)	11 (36.7)	0.0 (−0.2 to 0.3)	22	8 (36.4)	9 (40.9)	−0.1 (−0.4 to 0.1)
No INVEST	77	28 (36.4)	35 (45.5)	Reference	68	23 (33.8)	26 (38.2)	Reference	51	14 (27.5)	17 (33.3)	Reference
INVEST	26	11 (42.3)	14 (53.8)	−0.1 (−0.3 to 0.1)	22	8 (36.4)	8 (36.4)	0.0 (−0.2 to 0.3)	13	6 (46.2)	3 (23.1)	0.1 (−0.2 to 0.4)

continued

TABLE 12 Binary secondary outcomes (EQ-5D-5L) at 3, 6 and 12 months by randomised group and mean differences between HT and HTBF and no-INVEST and INVEST groups for those included in each of the final analysis models at the relevant time point (*continued*)

			3 months			6 months			12 months	
Binary outcome	***N***	**Indicating problems at baseline, *n* (%)**	**Indicating problems at follow-up, *n* (%)**	**Difference in proportions (95% CI)**	***N***	**Indicating problems at baseline, *n* (%)**	**Indicating problems at follow-up, *n* (%)**	**Difference in proportions (95% CI)**	***N***	**Indicating problems at baseline, *n* (%)**	**Indicating problems at follow-up, *n* (%)**	**Difference in proportions (95% CI)**
Pain/discomfort												
HT	43	37 (86.0)	32 (74.4)	Reference	38	33 (86.8)	27 (71.1)	Reference	29	25 (86.2)	20 (69.0)	Reference
HTBF	34	28 (82.4)	27 (79.4)	−0.0 (−0.2 to 0.1)	30	25 (83.3)	24 (80.0)	−0.1 (−0.3 to 0.1)	23	18 (78.3)	13 (56.5)	0.1 (−0.1 to 0.4)
No INVEST	77	65 (84.4)	59 (76.6)	Reference	68	58 (85.3)	51 (75.0)	Reference	52	43 (82.7)	33 (63.5)	Reference
INVEST	26	24 (92.3)	22 (84.6)	−0.1 (−0.2 to 0.1)	22	19 (86.4)	17 (77.3)	−0.0 (−0.2 to 0.2)	13	12 (92.3)	12 (92.3)	−0.3 (−0.5 to −0.1)
Anxiety/depression												
HT	43	26 (60.5)	24 (55.8)	Reference	38	23 (60.5)	20 (52.6)	Reference	29	18 (62.1)	16 (55.2)	Reference
HTBF	33	15 (45.5)	14 (42.4)	0.1 (−0.1 to 0.4)	30	12 (40.0)	14 (46.7)	0.1 (−0.2 to 0.3)	23	8 (34.8)	11 (47.8)	0.1 (−0.2 to 0.3)
No INVEST	76	41 (53.9)	38 (50.0)	Reference	68	35 (51.5)	34 (50.0)	Reference	52	26 (50.0)	27 (51.9)	Reference
INVEST	26	17 (65.4)	17 (65.4)	−0.2 (−0.4 to 0.1)	22	15 (68.2)	16 (72.7)	−0.2 (−0.4 to −0.0)	13	8 (61.5)	8 (61.5)	−0.1 (−0.4 to 0.2)

Note
The results under each time point summarise only the data from participants with recorded outcomes at both baseline and that follow-up time point.

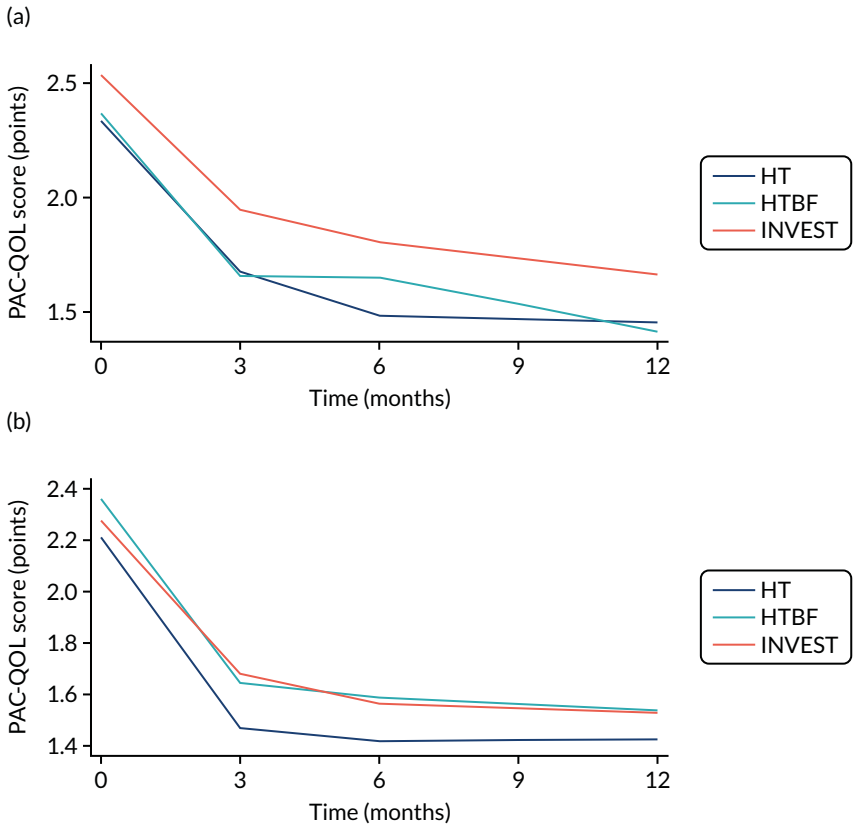

FIGURE 10 Average PAC-QoL score over time in months for (a) all participants ($n = 178$); and (b) those with no missing data ($n = 54$). Both show reductions in score (i.e. improvement) over time.

TABLE 13 The CapaCiTY trial 1 AEs and SAEs

Variable	HT ($N = 68$)	HTBF ($N = 68$)	No INVEST ($N = 136$)	INVEST ($N = 46$)	Total ($N = 182$)
Related AEs					
Number of patients reporting AE	4	4	8	5	13
Number of AEs reported by category					
Abdominal pain	0	0	0	0	0
Anal/rectal pain or discomfort	0	2	2	1	3
Bloating	0	0	0	0	0
Constipation	0	0	0	0	0
Haemorrhoids	0	0	0	0	0
Loose motions	0	2	2	0	2
Rectal bleeding	3	2	5	5	10
Vaginal/perineal bulge	0	0	0	0	0
Miscellaneous	1	0	1	2	3
Severity					
Mild	2	2	4	5	9
Moderate	2	4	6	3	9
Severe	0	0	0	0	0

continued

TABLE 13 The CapaCiTY trial 1 AEs and SAEs (*continued*)

Variable	HT (*N* = 68)	HTBF (*N* = 68)	No INVEST (*N* = 136)	INVEST (*N* = 46)	Total (*N* = 182)
Action					
No action taken	1	3	4	5	9
Withdrawal	0	0	0	1	1
Concomitant medication	1	1	2	2	4
Non-drug therapy	1	2	3	0	3
SAEs[a]					
Number of patients reporting SAE	0	0	0	2	2
Number of SAEs reported that require hospitalisation or prolongation of existing hospitalisation	0	0	0	2	2
Causality					
Unlikely to be related	0	0	0	2	2
Related	0	0	0	0	0
Expectedness					
Expected	0	0	0	0	0
Unexpected	0	0	0	2	2
Action taken					
Withdrawal	0	0	0	1	1
None	0	0	0	1	1

a None of the SAEs was identified as related to a treatment; no unresolved SAEs were reported.

TABLE 14 The CapaCiTY trial 1 economic analysis variables (£, 2018)

	HT (*N* = 68 patients)			HTBF (*N* = 68 patients)			INVEST (*N* = 46 patients)		
Variable	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***
Resource use									
Intervention									
Duration of visits (minutes)	140	80	57	152	102	61	143	85	39
Number of biofeedback sessions	–	–	–	2.09	1.43	67	0.93	1.35	44
Invest procedure completed	–	–	–	–	–	–	0.93	0.33	46
Number of prescriptions	2.00	1.98	48	1.43	1.97	46	1.53	1.62	40
0–3 months									
Number of prescriptions	0.48	0.70	44	0.83	1.42	36	0.52	1.09	27
GP visits	0.02	0.15	44	0.14	0.35	36	0.11	0.32	27
District nurse visits	0.02	0.15	44	0.00	0.00	36	0.00	0.00	27
Pharmacist visits	0.05	0.21	44	0.06	0.23	36	0.15	0.46	27
A&E visits	0.00	0.00	44	0.03	0.17	36	0.00	0.00	27
Outpatient visits	0.20	0.51	44	0.08	0.28	36	0.15	0.46	27
Days from work	0.98	2.65	44	0.64	1.73	36	2.59	5.80	27
Inpatient visits	0.00	0.00	43	0.11	0.68	35	0.00	0.00	27

TABLE 14 The CapaCiTY trial 1 economic analysis variables (£, 2018) (*continued*)

	HT (*N* = 68 patients)			HTBF (*N* = 68 patients)			INVEST (*N* = 46 patients)		
Variable	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***
4–6 months									
Number of prescriptions	0.54	1.00	39	0.37	0.61	30	0.32	0.78	22
GP visits	0.18	0.60	39	0.17	0.59	30	0.14	0.47	22
District nurse visits	0.00	0.00	39	0.00	0.00	30	0.00	0.00	22
Pharmacist visits	0.08	0.35	39	0.17	0.59	30	0.05	0.21	22
A&E visits	0.00	0.00	39	0.00	0.00	30	0.00	0.00	22
Outpatient visits	0.18	0.72	39	0.10	0.31	30	0.14	0.35	22
Days from work	3.51	12.72	39	0.86	2.26	29	1.95	5.72	22
Inpatient visits	0.03	0.16	39	0.00	0.00	30	0.00	0.00	21
7–12 months									
Number of prescriptions	0.48	0.89	31	0.33	0.64	24	1.15	1.46	13
GP visits	0.27	0.64	30	0.29	0.91	24	0.46	1.66	13
District nurse visits	0.07	0.37	30	0.00	0.00	24	0.00	0.00	13
Pharmacist visits	0.03	0.18	30	0.00	0.00	24	0.54	1.66	13
A&E visits	0.10	0.55	30	0.00	0.00	24	0.08	0.28	13
Outpatient visits	0.10	0.55	30	0.42	1.32	24	0.38	1.39	13
Days from work	2.30	6.72	30	1.08	3.08	24	4.00	11.48	13
Inpatient visits	0.00	0.00	30	0.04	0.21	23	0.00	0.00	13
Health-care cost									
–3 to 0 months (intervention)	326	186	57	493	322	61	804	351	39
0–3 months	42	87	43	55	137	35	35	75	27
4–6 months	59	152	39	26	51	30	25	51	21
7–12 months	57	142	30	132	320	23	147	283	13
Overall	506	205	19	815	411	17	988	269	9
Societal cost									
Overall	1187	1866	19	1231	1016	17	1312	665	9
EQ-5D-5L									
–3 months	0.664	0.308	68	0.693	0.247	66	0.679	0.223	45
3 months	0.652	0.329	43	0.708	0.261	33	0.665	0.211	26
6 months	0.733	0.251	38	0.681	0.272	29	0.642	0.256	22
12 months	0.737	0.262	29	0.734	0.289	22	0.713	0.136	13
QALYs									
–3 to 12 months	0.874	0.357	23	0.842	0.345	19	0.897	0.171	11

Notes
Subtotals may not sum to totals because of different numbers of participants contributing.
Intervention occurred in the 3 months preceding the trial baseline, when follow-up commenced.
Days from work included in societal cost but not NHS cost.
The QALY estimates reported cover 15 months and are undiscounted in this table.

Cost-effectiveness analyses

The base-case model is reported in *Table 15*. Compared with HT, both HTBF and INVEST-guided treatment were estimated to be associated with higher costs and lower QoL, making HT the dominant strategy. In both instances cost increases were significant (HTBF vs. HT: £239, 95% CI £133 to £354; INVEST vs. HT: £543, 95% CI £403 to £685), and QoL decrements were small for HTBF (–0.010 QALYs, 95% CI –0.053 to 0.03 QALYs) and more significant for INVEST (–0.047 QALYs, 95% CI –0.093 to –0.001 QALYs), compared with HT. These findings are presented in *Figure 11*. On the ICER plane, credible regions are plotted around median ICERs reflecting where 95% of bootstrapped estimates lie. Incremental differences comparing HTBF and INVEST are not presented because both are dominated by HT. NMB values were negative for HTBF and INVEST across the commonly used range of WTP thresholds, indicating lack of cost-effectiveness (see *Table 15*). These findings are presented as CEACs at varying WTP thresholds, showing the probability of each intervention being cost-effective. At the NICE threshold of £30,000 per QALY, the probability that HT is the most cost-effective alternative is 83%. The EVPI values the opportunity loss of ongoing uncertainty. At a WTP threshold of £30,000 per QALY, the EVPI per subject is £59. There are no reliable British figures for the incidence, prevalence or chronic idiopathic constipation requiring hospital management or a future timeline for relevant new research. Assuming that an approximate cost of a further definitive RCT is £1M, the research would need to benefit only ≈ 17,000 patients, which might indicate that further research is merited, particularly if the findings have international relevance.

TABLE 15 The CapaCiTY trial 1 cost-effectiveness analysis (£, 2018)

Variable	ICER (95% CI)	IC (95% CI)	IQ (95% CI)	CEAC *p*-value[a]	CEAC *p*-value[b]	NMB[a] (95% CI)	NMB[b] (95% CI)	EVPI[b]
Base case								
HTBF vs. HT	[c] (7506 to [c])	239 (133 to 354)	–0.010 (–0.053 to 0.03)	0.098	0.168	–402 (–1058 to 219)	–565 (–1858 to 665)	59
INVEST vs. HT	[c] ([c] to [c])	543 (403 to 685)	–0.047 (–0.093 to –0.001)	0.001	0.002	–1241 (–1962 to –539)	–1939 (–3338 to –564)	–
Complete case								
HTBF vs. HT	[c] (3777 to [c])	340 (135 to 578)	–0.016 (–0.121 to 0.076)	0.142	0.174	–620 (–2206 to 798)	–897 (–4026 to 1906)	609
INVEST vs. HT	[c] (3848 to [c])	542 (351 to 764)	–0.005 (–0.156 to 0.124)	0.230	0.304	–670 (–2934 to 1357)	–793 (–5262 to 3259)	–
Sensitivity analysis 1[d]								
HTBF vs. HT	[c] (73,105 to [c])	615 (536 to 695)	–0.031 (–0.074 to 0.008)	0.001	0.005	–1092 (–1761 to –468)	–1570 (–2885 to –330)	1
INVEST vs. HT	[c] ([c] to [c])	744 (624 to 875)	–0.069 (–0.113 to –0.021)	0.000	0.000	–1777 (–2454 to –1079)	–2809 (–4149 to –1394)	–
Sensitivity analysis 2[e]								
HTBF vs. HT	[c] (11,439 to [c])	246 (136 to 365)	–0.024 (–0.073 to 0.019)	0.041	0.081	–621 (–1382 to 64)	–996 (–2468 to 335)	25
INVEST vs. HT	[c] ([c] to [c])	532 (407 to 652)	–0.053 (–0.102 to –0.002)	0.000	0.001	–1325 (–2077 to –566)	–2119 (–3609 to –617)	–

a Probability cost-effective at WTP threshold of £15,000 per QALY.
b Probability cost-effective at WTP threshold of £30,000 per QALY.
c Denotes a dominated strategy: increase in cost and decrease in QALYs.
d Non-recoverable cost assumption.
e Non-participants (zero intervention cost patients) excluded.

Notes
Bootstrapped 95% CIs; median ICERs.
Base-case and sensitivity analyses: imputed with 60 draws; assuming MAR.
Complete case: includes only participants with complete cost and QALY data; assuming missing completely at random.

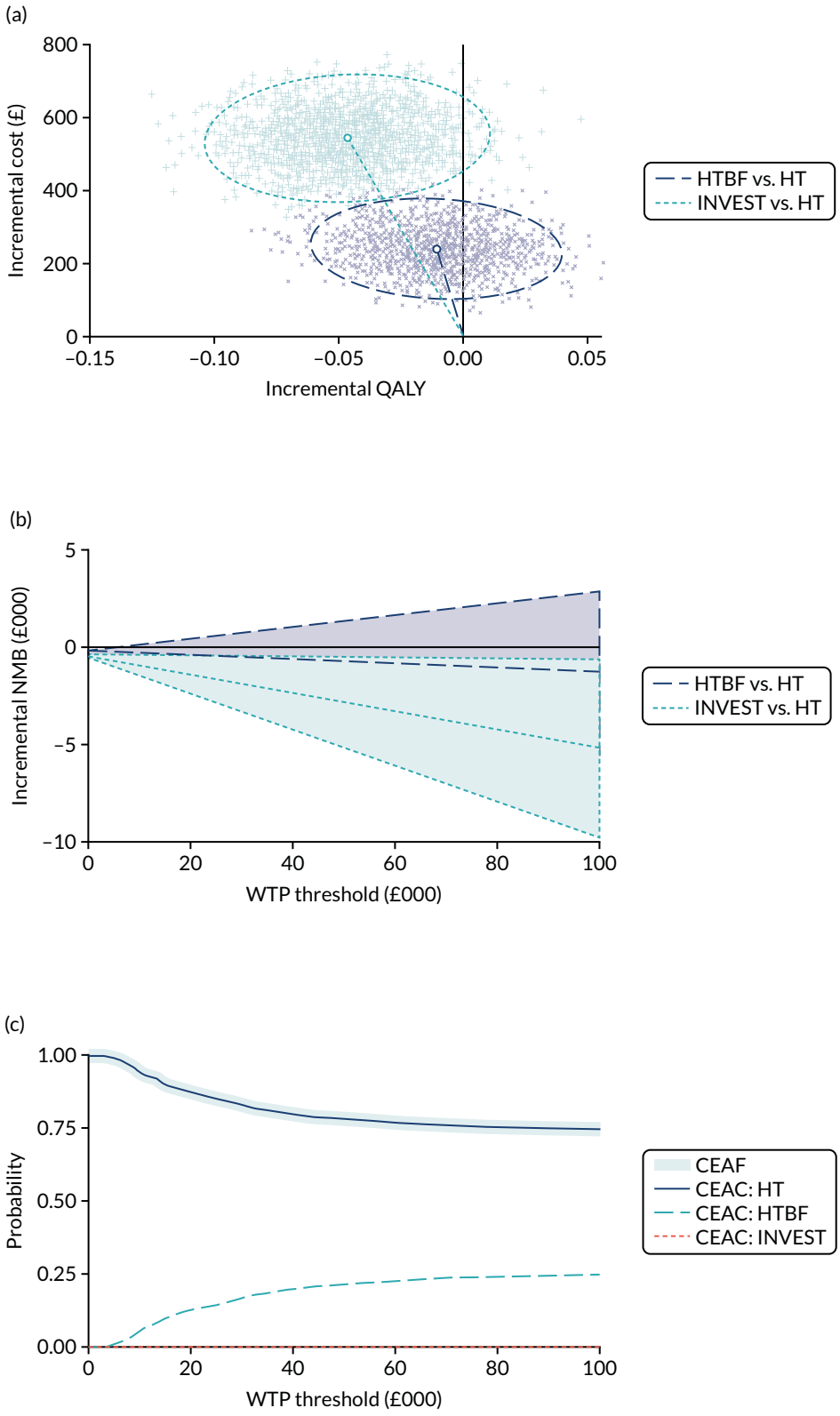

FIGURE 11 The CapaCiTY trial 1 cost-effectiveness analysis: base case. (a) ICER plane [the average ICER for each intervention (compared with HT) is shown as a line from the origin and the credible regions (dashed circles) show where 95% of estimates lie]; (b) incremental NMB (the shaded regions are the corresponding 95% CIs); (c) CEACs and CEAF; and (d) EVPI. (*continued*)

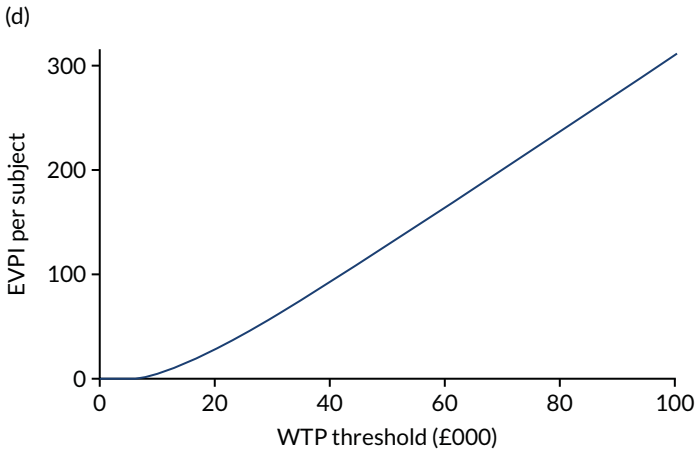

FIGURE 11 The CapaCiTY trial 1 cost-effectiveness analysis: base case. (a) ICER plane [the average ICER for each intervention (compared with HT) is shown as a line from the origin and the credible regions (dashed circles) show where 95% of estimates lie]; (b) incremental NMB (the shaded regions are the corresponding 95% CIs); (c) CEACs and CEAF; and (d) EVPI.

In *Figure 11a* the ICER plane shows the bootstrapped distribution of estimated incremental costs and QALYs comparing HTBF or INVEST with HT. Bootstrapping is a method of resampling the trial data to mimic conducting many trials; the range of findings reflects the uncertainty in the trial. The average ICER for each intervention (compared with HT) is shown as a line from the origin. The credible regions (dashed circles) show where 95% of estimates lie. Compared with HT, average costs increase for both HTBF and INVEST and QALYs decrease, meaning that HT is the dominant treatment strategy. In *Figure 11b* the incremental NMB describes the resource gain (or loss) when investing in HTBF or INVEST. The shaded regions are the corresponding 95% CIs. Investing in HTBF or INVEST at any threshold WTP would impose a loss to the health system when compared with other alternative choices. In *Figure 11c* the presentation of CEACs re-presents the incremental NMB findings as the probability that each intervention is cost-effective at different WTP thresholds. The CEAF is a necessary further analysis when three or more interventions are compared. Although HT is the dominant strategy the finding is uncertain, being estimated to be correct with a probability of 83% at a WTP threshold of £30,000 per QALY. In *Figure 11d* the EVPI indicates the value to a health-care system of further research to eliminate uncertainty, as WTP varies.

The complete-case analysis is also presented in *Table 15*. Although the numbers contributing are small, the findings are similar to the base case, if less precise. The base-case analysis costed the intervention received by each participant in terms of the number of scheduled visits attended, time taken and equipment used. This assumes no resource losses due to non-attendance or cancellation. A first post hoc sensitivity analysis costed each intervention fully per protocol, assuming that these were non-recoverable costs. The consequence is that the incremental cost of HTBF and INVEST increases, increasing the probability that HT is cost-effective ($p > 99\%$ at a WTP threshold of £30,000 per QALY). A minority of patients (12%) had no record of engaging in the trial intervention. In a second post hoc sensitivity analysis, these subjects were removed to explore a participant analysis and reduce the imputation burden. Findings were similar to and thus supportive of the base-case findings.

Results: patient experience and qualitative analysis

Emergent themes are presented in this section. Numbers in square brackets refer to the numbered quotations in *Appendix 2, Quotations from participants contributing to qualitative analysis in all three trials, CapaCiTY trial 1: habit training with or without biofeedback with or without standardised radiophysiological investigations*.

INVEST compared with no INVEST

For those randomised to the INVEST tests, some felt embarrassment, especially if the health-care professional was of a different sex from the patient. However, some patients did not seem to mind the

tests, particularly because they felt that the health-care team managed the investigations professionally and with dignity. Several were relieved to have been in the INVEST group because they felt that the tests provided more information about potential sources of their constipation. The tests also gave some reassurance that no underlying diseases were the root cause of their constipation, providing a sense of closure and peace of mind [1].

Many patients randomised to the no-INVEST group were disappointed not to have received the tests because they felt that the investigations would aid in pinpointing underlying issues that were contributing to their CC. In addition, some patients thought that having visualisation of their gut would help them to better understand their bodily issues. The desire of patients to have the tests was also noticed by staff delivering the intervention.

For a few patients, not having the prior testing was not an issue. Some patients had mixed feelings in terms of not being allocated to the INVEST group; some were pleased that they did not have to experience the embarrassment or invasiveness of the procedures. They also initially believed that they would have received better care had they been in the INVEST group [2]. Others felt some regret at not having tests but appeared to accept it and move on.

Habit training only

Some patients were initially disappointed when they discovered that they were in the HT group because they did not believe that HT on its own would be of benefit. For others, being placed in this group provided a sense of encouragement. For many patients the best thing about HT was being able to talk to an interested professional during the sessions about their constipation, particularly because they considered this a taboo subject [3]. Being able to speak about their issues helped to normalise the experience of CC [4].

A number of patients found that the HT helped them to better understand how diet and fluids influence their constipation [5]. Those who had the additional biofeedback element often felt that the HT elements were the most important [6]. Patients reported better knowledge of the types of foods that helped or worsened constipation. However, a few patients did not find changes in their diet beneficial or their diet already followed the HT advice. Some patients noted that learning to breathe and push correctly during defaecation helped them to pass stools more easily [7]. However, a few struggled with utilising this breathing technique.

Some patients also noted that learning how their bowels worked allowed them to better understand their own bodies [8]. Learning was enhanced by visual aids in the booklet; staff echoed the usefulness of the booklet [9]. HT also allowed more time than HTBF for education during the sessions. Some patients stated that being taught how to sit on the toilet and for how long, and/or using a stool to elevate their legs, was helpful [9]. Others did not find the advice about sitting worked for them, or they did not comply with the advice.

Several patients stated how helpful and supportive they found the staff. Many found that the programme helped them to focus on their constipation and the potential solutions without reverting to over-reliance on laxatives [11]. Some felt that HT took considerable time and dedication to start seeing improvements; others stated that carrying out the HT methods on a regular basis was difficult or painful to maintain without laxatives. For those who found HT helpful, benefits ranged from some improvement [12] to substantial improvement [13].

Habit training with biofeedback

For patients who had the additional biofeedback element, some stated that they found the visual information on the screen helpful [13]; some staff echoed the visual benefit of biofeedback. Some patients in the HTBF group saw a substantial improvement, whereas others did not appear to see much benefit.

Staff opinions were mixed regarding the HTBF intervention, with some suggesting that biofeedback helped patients improve more than HT. However, others felt that biofeedback machines offered little in terms of improving patient symptoms [14]. Some patients found the HTBF sessions a little embarrassing because a probe needed to inserted into the anus [15]. For others the worst thing about biofeedback was that they did not find that it helped their symptoms. Therefore, a few of the patients seem to believe that their constipation would never improve. For clinical staff, seeing patients' constipation problems improve was the most satisfying aspect for them, whether that was with HT or HTBF. However, it was frustrating for staff when interventions did not work, particularly for patients who had had symptoms for many years.

Maintaining learning

Many patients who saw benefits from HT or HTBF are continuing to implement what they learned, whether that is diet and fluid maintenance, using a footstool and/or utilising breathing exercises. A few patients reported that they still took laxatives either on occasion or regularly to help their constipation. However, others reported that they no longer needed laxatives [16].

When asked whether or not they would recommend HT, many stated that they would. Some people would recommend HTBF [17] and a few would recommend HT but not HTBF. A few would recommend one HT session but not multiple sessions because they did not find it beneficial enough. For others, even if the programme did not work for them in the way that they had hoped, they would still recommend to others with constipation that they try it.

Staff experience of delivering the intervention

Many staff indicated that the intervention was not difficult to deliver, particularly the HT aspect for nursing staff, because this was their main clinical role prior to the study. However, time spent filling in paperwork, setting up rooms, arranging biofeedback machines and organising a clinical scientist to be present (if one was needed to help with setting up and operating the biofeedback machine) had an impact on their workload, adding 10–20 minutes to their usual consultation time per patient [18].

Regarding the use of biofeedback machines, staff ranged in their confidence levels depending on whether or not they had:

- additional professional support such as a clinical scientist
- enough previous experience using the same biofeedback machine [19]
- used the machine on a regular basis
- received formal training.

Although training sessions were provided to staff, a few staff did not receive formal biofeedback training at their site and had to rely on the protocol description. Missing formal training may have contributed to the reduction in confidence levels among some staff members. Staff lack of confidence utilising the machines may have affected the patient experience during biofeedback.

Feedback on the study/treatment design

Some patients felt that the study/treatment plan was well designed and did not believe that the intervention could be improved in any way, even if it did not address their needs specifically. Many patients stated that the number and duration of sessions were right. However, some reported that the time between sessions felt like long periods without support. A few mentioned that they would have liked more information about their INVEST results.

Many patients and staff mentioned stress and psychological issues related to constipation, and specific recommendations were made about addressing this aspect more directly in future roll-outs of the intervention. A number of patients and staff mentioned that lying down during the biofeedback sessions seemed counterintuitive to retraining their muscles for a bowel emptying process that is carried out sitting up. Some patients found the information in the HT sessions too basic for their situation or felt patronised and would have preferred a more tailored approach.

Patient discontinuation

Four of the 24 patients interviewed for CapaCiTY trial 1 reported that they had discontinued their participation in the intervention because of:

- unsuitability for the study (e.g. having an anal fissure)
- misunderstanding what the study could provide, such as expecting to be placed into a group for surgery
- the intervention not appearing to work/constipation symptoms returning
- fear of stopping laxative and suppository use.

CapaCiTY trial 2: pragmatic randomised trial of low-volume compared with high-volume initiated transanal irrigation therapy in adults with chronic constipation

Intervention

Transanal irrigation training was provided by a trained nurse or physiotherapist with experience in delivering care for CC. A standardised approach and intervention was provided via use of an intervention manual.

The course of therapy included a nurse-led training session (or multiple sessions if required to ensure that the device was being used effectively) followed by patient-led home TAI therapy. The low-volume system commonly used in practice was Qufora® IrriSedo Mini (MacGregor Healthcare Ltd, Tranent, UK). Various commercially available high-volume systems could be used, including Peristeen® Anal Irrigation System (Coloplast A/S, Humlebæk, Denmark) and Qufora IrriSedo Balloon (MacGregor Healthcare Ltd).

Low-volume transanal irrigation

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

High-volume transanal irrigation

High-volume systems consist of an irrigation bag connected to a tube. The water flows into the rectum either by gravity or using a pump. Some systems employ a balloon to hold the device in place during irrigation; others require the patient to hold it in place. The mechanism of action is the same for all systems. Initial frequency of TAI is the same as for low-volume TAI (i.e. daily for 14 days, then on alternate days). Patients will commence with irrigations of 300 ml and increase this by 100 ml every 2 days until satisfactory defaecation is achieved or the procedure becomes uncomfortable, up to a maximum of 1500 ml. Patients may adjust therapy depending on response, as for low-volume TAI.

Design features

Basic design

Robust data for the use of irrigation therapy in chronic (idiopathic) constipation are lacking. In addition, there are no data demonstrating superiority of high-volume over low-volume systems. Given differences in cost between the two systems, a randomised study of well-characterised patients comparing the two methods would provide useful information on whether or not one system holds a clear advantage over the other. In addition, the short- and long-term efficacy and acceptability of therapy in CC could be evaluated.

Patients used one system only (plus defined 'rescue therapies') for a minimum of 3 months. After this time point they could switch to the other system if their initial therapy was ineffective/unsatisfactory. Thus, consenting patients were randomised to initiate therapy with one of these systems but had the option of switching to the other after an initial 3-month period. This allowed identification of response rates to each system in the short term (3 months) and thereafter a comparison between treatment strategies (low-volume vs. high-volume initiated therapy) rather than a pure comparison of the two techniques. This was a patient-centred study design aiming to limit the time patients spent using ineffective therapy without being allowed to try an alternative. Reasons for switching were captured qualitatively (see *Patient experience*).

Switching TAI systems before completing the 3-month waiting period was discouraged and, if it occurred, was documented as a protocol violation, with the timing and reason documented. If symptoms were severe despite the use of TAI and rescue therapies then other medications could be used on compassionate grounds, but these were also recorded in the CRF/concomitant medications log.

Sample size calculation

The PAC-QoL is a 28-item disease-specific measure, with each item scoring 0–4 points, providing an aggregate score 0.0–4.0 points. Superiority of either low-volume or high-volume TAI could be demonstrated by a difference in effect size of 0.4 points, with a variance estimate conservatively set at SD = 1 point from the published literature. To detect an effect size of 0.4 points (mean/SD = 0.4 points) between the two groups with 90% power and 5% significance at 3 months requires 133 patients per group and 266 in total. Allowing for an anticipated 10% loss to follow-up, we planned to recruit 300 patients.

Randomisation procedure

Patients were randomised 1 : 1 into two groups: those to commence therapy with a low-volume device and those to commence therapy with a high-volume device. Because male patients represent a minority of patients with CC (≈ 10%) and there may be differences in pathophysiology (and therefore possibly response) between male and females patients, patients were stratified by sex and female patients by centre.

Blinding

Patients and clinicians were necessarily aware of treatment allocations. The need to collect data on frequency and volume of TAI, as well as reasons for discontinuing or switching between systems, meant that assessor blinding was not possible with respect to these outcomes. Any researcher collecting CRFs or handling journals was therefore unblinded. However, the primary outcome (PAC-QoL score at 3 months) was concealed: patients completed this questionnaire without a researcher present and placed it in a sealed envelope.

Concomitant medications

Methods as in CapaCiTY trial 1, with recorded ad libitum usage.

Statistical methods

The primary outcome, PAC-QoL score, was analysed as a continuous variable on an ITT basis; that is, all patients for whom an outcome was available at 3 months were included in the analysis, and analysed according to the treatment group to which they were originally randomised (even though two patients crossed over before the primary outcome was measured).

We present descriptive statistics (i.e. mean, SD, median and IQR) by trial group. Owing to the small numbers of patients providing the outcome data at follow-up, no statistical comparisons were performed.

All secondary outcomes were also analysed on an ITT basis. For each outcome we present descriptive statistics (as appropriate) by trial group; continuous variables (e.g. PAC-QoL score) have been summarised by treatment group using mean, SD, median and IQR. For categorical variables, numbers and percentages of patients reporting each response option have been presented by trial group.

Note that irrigation volume transgresses the ITT rule, being reported as that actually being used despite original allocation. Results obtained using the CC-BRQ and BIPQ-CC have been omitted pending further analysis.

Time to cessation of TAI is presented using Kaplan–Meier graphs, and where available reasons for cessation of each system presented.

For cost-effectiveness, patients were randomised in parallel trial groups to low-volume or high-volume TAI therapy. Days of use of low-volume and high-volume TAI were not recorded directly but approximated from available data for using evidence of use in each follow-up period, frequency of use (days per week) in each period and withdrawal data. No discounting was applied to economic data reflecting the follow-up period of 1 year.

Recruitment

First recruitment and intervention was on 11 November 2015; recruitment ended 30 June 2018. A total of 65 patients (target 300 patients) were randomised out of 150 screened (21.7%) from seven sites. Reasons for screen failure are shown in *Figure 12*. Three sites opened but failed to recruit; the remainder randomised 1–33 patients, with approximately half of the patients recruited from secondary care and half from tertiary care. A total of 65 patients were randomised. A total of 14 patients withdrew from the study before the primary end point (51 completed the 3-month follow-up). A total of 30 patients were randomised to low-volume TAI and 35 to high-volume TAI. The CONSORT flow diagram is shown in *Figure 4*.

Baseline characteristics

Table 16 shows the numbers and percentages of patients with baseline characteristics presented by trial group. Continuous variables (e.g. age) were summarised by treatment group using mean and SD (median and IQR if non-normally distributed). The data show that half of the patients were in tertiary care and that, as would be expected, all had tried lifestyle measures and laxatives. The age and sex distribution are as would be expected from a hospital-based constipation cohort. The prevalence of other medical conditions was fairly typical for any hospital-attending patient group of this age range with a chronic illness. One-quarter of patients had hypermobility, higher than reported in the general population.

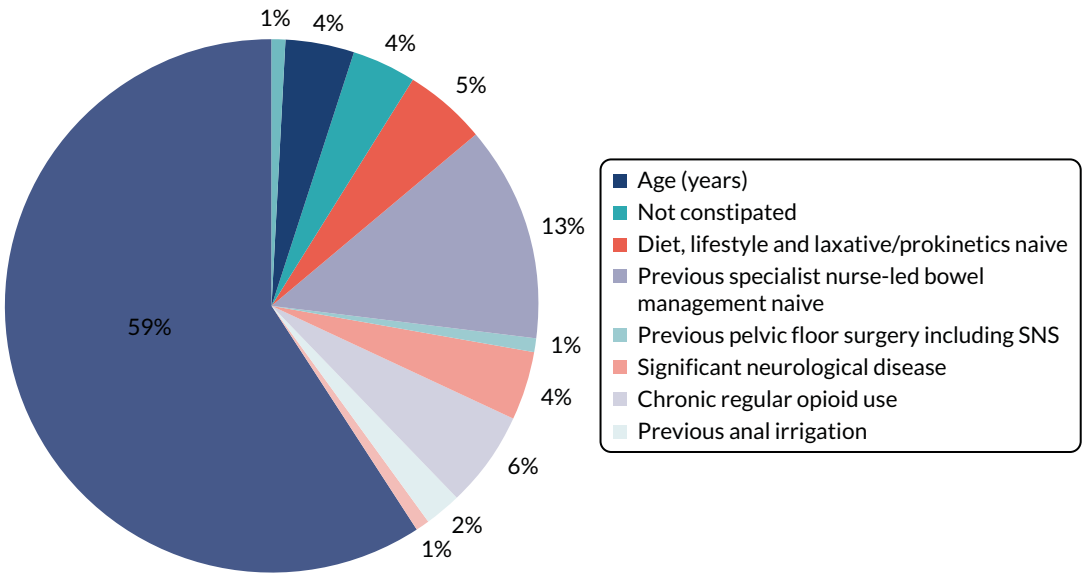

FIGURE 12 The CapaCiTY trial 2 screen failures. SNS, sacral nerve stimulation.

TABLE 16 The CapaCiTY trial 2 baseline data

Characteristic	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
Referral method*, n *(%)			
Secondary care	11 (36.7)	16 (45.7)	27 (41.5)
Tertiary care	16 (53.3)	18 (51.4)	34 (52.3)
Other	3 (10.0)	1 (2.9)	4 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Demographic characteristic			
Sex, *n* (%)			
Male	3 (10.0)	4 (11.4)	7 (10.8)
Female	27 (90.0)	31 (88.6)	58 (89.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, *n* (%)			
Asian	1 (3.3)	1 (2.9)	2 (3.1)
Black	2 (6.7)	1 (2.9)	3 (4.6)
Mixed	0 (0.0)	2 (5.7)	2 (3.1)
White	26 (86.7)	31 (88.6)	57 (87.7)
Missing	1 (3.3)	0 (0.0)	1 (1.5)
Age (years)			
Mean (SD)	43.3 (15.0)	44.9 (11.8)	44.2 (13.3)
Median (IQR)	41.5 (37.0–55.0)	43.0 (40.0–53.0)	43.0 (39.0–54.0)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Past medical history*, n *(%)			
Total	27 (90.0)	28 (80.0)	55 (84.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular condition	8 (26.7)	6 (17.1)	14 (21.5)
Heart disease	1 (3.3)	0 (0.0)	1 (1.5)
Hypertension	5 (16.7)	4 (11.4)	9 (13.8)
Hypercholesterolaemia	5 (16.7)	3 (8.6)	8 (12.3)
Other	1 (3.3)	1 (2.9)	2 (3.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory condition	10 (33.3)	7 (20.0)	17 (26.2)
Asthma	9 (30.0)	7 (20.0)	16 (24.6)
COPD	3 (10.0)	1 (2.9)	4 (6.2)
Other	1 (3.3)	1 (2.9)	2 (3.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal condition	15 (50.0)	12 (34.3)	27 (41.5)
IBS	11 (36.7)	7 (20.0)	18 (27.7)
Crohn's disease	0 (0.0)	0 (0.0)	0 (0.0)
Ulcerative colitis	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	1 (2.9)	1 (1.5)
Colonic polyps	3 (10.0)	3 (8.6)	6 (9.2)
Other	4 (13.3)	3 (8.6)	7 (10.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

TABLE 16 The CapaCiTY trial 2 baseline data (*continued*)

Characteristic	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
Metabolic condition	8 (26.7)	4 (11.4)	12 (18.5)
Diabetes	5 (16.7)	2 (5.7)	7 (10.8)
Hypothyroidism	2 (6.7)	3 (8.6)	5 (7.7)
Hyperthyroidism	1 (3.3)	0 (0.0)	1 (1.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Haematological condition	2 (6.7)	0 (0.0)	2 (3.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic condition	2 (6.7)	3 (8.6)	5 (7.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Renal disease	1 (3.3)	0 (0.0)	1 (1.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Genito-urinary condition	6 (20.0)	7 (20.0)	13 (20.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Neurological/CNS condition	10 (33.3)	7 (20.0)	17 (26.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric condition	12 (40.0)	12 (34.3)	24 (36.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Dermatological condition	6 (20.0)	6 (17.1)	12 (18.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal condition	4 (13.3)	5 (14.3)	9 (13.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Other condition	3 (10.0)	1 (2.9)	4 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Past surgical history*, n *(%)			
Total	17 (56.7)	17 (48.6)	34 (52.3)
Abdominal operation	10 (33.3)	7 (20.0)	17 (26.2)
Gynaecological procedure	10 (33.3)	11 (31.4)	21 (32.3)
Proctological or perineal procedure	2 (6.7)	5 (14.3)	7 (10.8)
Neuromodulation	1 (3.3)	0 (0.0)	1 (1.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Duration (months) of constipation symptoms			
Mean (SD)	90.4 (79.1)	120.7 (76.3)	106.7 (78.5)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Previous lifestyle modifications*, n *(%)			
Total	30 (100.0)	35 (100.0)	65 (100.0)
Diet	30 (100.0)	35 (100.0)	65 (100.0)
Fluid	30 (100.0)	35 (100.0)	65 (100.0)
Exercise	27 (90.0)	31 (88.6)	58 (89.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 16 The CapaCiTY trial 2 baseline data (*continued*)

Characteristic	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
Alternative therapies*, n *(%)			
Total	5 (16.7)	8 (22.9)	13 (20.0)
Missing	0 (0.0)	1 (2.9)	1 (1.5)
Laxatives*, n *(%)			
Total	30 (100.0)	34 (97.1)	64 (98.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Antidiarrhoeals*, n *(%)			
Total	1 (3.3)	2 (5.7)	3 (4.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Prokinetics*, n *(%)			
Total	18 (60.0)	23 (65.7)	41 (63.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Nurse-led bowel management*, n *(%)			
Total	30 (100.0)	35 (100.0)	65 (100.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Family history of bowel disease*, n *(%)			
IBS	7 (23.3)	5 (14.3)	12 (18.5)
IBD	2 (6.7)	3 (8.6)	5 (7.7)
Gastrointestinal cancer	7 (23.3)	5 (14.3)	12 (18.5)
Other	4 (13.3)	5 (14.3)	9 (13.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sexual history (female participants only)*, n *(%)			
Sexually active	14 (51.9)	23 (74.2)	37 (63.8)
Child-bearing potential	18 (66.7)	19 (61.3)	37 (63.8)
> 1 year post menopausal	4 (14.8)	7 (22.6)	11 (19.0)
Surgically sterile	7 (25.9)	9 (29.0)	16 (27.6)
Contraceptive use (female participants only)*, n *(%)			
Barrier	12 (44.4)	14 (45.2)	26 (44.8)
Non-barrier	2 (7.4)	6 (19.4)	8 (13.8)
Missing	11 (40.7)	8 (25.8)	19 (32.8)
Past obstetric history (female participants only)			
Total, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Number of vaginal deliveries, mean (SD)	19 (70.4)	25 (80.6)	44 (75.9)
Number of caesareans, mean (SD)	0 (0.0)	0 (0.0)	0 (0.0)
Number of forceps/ventouse deliveries, mean (SD)	1.9 (1.1)	2.3 (1.3)	2.1 (1.3)
Number of episiotomies, mean (SD)	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
Number of obstetric tears, mean (SD)	0.5 (0.7)	0.4 (0.9)	0.4 (0.8)
Missing, *n* (%)	0.7 (0.9)	0.3 (0.5)	0.5 (0.7)

TABLE 16 The CapaCiTY trial 2 baseline data (*continued*)

Characteristic	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
Faecal incontinence symptoms*, n *(%)			
Total	0.6 (1.0)	0.6 (0.9)	0.6 (0.9)
Faecal urgency	0 (0.0)	0 (0.0)	0 (0.0)
Urge faecal incontinence	17 (56.7)	17 (48.6)	34 (52.3)
Passive faecal incontinence	9 (30.0)	14 (40.0)	23 (35.4)
Post defaecation leakage	5 (16.7)	7 (20.0)	12 (18.5)
Difficulty wiping clean	2 (6.7)	8 (22.9)	10 (15.4)
Missing	4 (13.3)	8 (22.9)	12 (18.5)
Pelvic organ prolapse symptoms*, n *(%)			
Total	7 (23.3)	9 (25.7)	16 (24.6)
Vaginal bulging	0 (0.0)	0 (0.0)	0 (0.0)
External rectal prolapse	0 (0.0)	0 (0.0)	0 (0.0)
External uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
In what proportion of bowel motions does the patient experience spontaneous rectal urge to defaecate (without laxatives)?*, n *(%)			
Never	10 (33.3)	9 (25.7)	19 (29.2)
< 25%	10 (33.3)	12 (34.3)	22 (33.8)
25–75%	5 (16.7)	7 (20.0)	12 (18.5)
> 75%	2 (6.7)	1 (2.9)	3 (4.6)
Always	2 (6.7)	5 (14.3)	7 (10.8)
Missing	1 (3.3)	1 (2.9)	2 (3.1)
Joint hypermobility*,[a] n *(%)			
Total	8 (26.7)	9 (25.7)	17 (26.2)
Missing	1 (3.3)	2 (5.7)	3 (4.6)

COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.
a Hypermobility was indicated by a response of 'yes' to two or more out of five questions used to assess joint hypermobility.

Table 17 shows the data for outcome measures at baseline. These were comparable between the two groups for all major characteristics.

Results: clinical effectiveness

Owing to the low numbers of patients recruited, only descriptive statistics are presented (*Table 18*). At 3 months there was a modest reduction of mean PAC-QoL score from 2.4 to 2.2 points (0.2-point reduction) in the low-volume irrigation group and a larger reduction of 0.5 points in the high-volume TAI group. Although the difference is not large there was consistency of findings across some of the other outcome measures. Secondary outcomes are shown in *Tables 19* and *20*. For example, global satisfaction, global improvement and EQ-VAS scores were more improved in the high-volume TAI group. These results were based on an ITT analysis and, therefore, included two patients who crossed over before 3 months (possibly diluting the difference in effect).

TABLE 17 The CapaCiTY trial 2 outcome measure data at baseline

Outcome measure	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
PAC-QoL score (points)			
Overall, mean (SD)	2.5 (0.8)	2.4 (0.7)	2.4 (0.8)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Dissatisfaction, mean (SD)	3.3 (0.6)	3.2 (0.6)	3.3 (0.6)
Missing, *n* (%)	2 (6.7)	3 (8.6)	5 (7.7)
Physical discomfort, mean (SD)	2.7 (0.9)	2.7 (0.8)	2.7 (0.8)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Psychosocial discomfort, mean (SD)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Worries and concerns, mean (SD)	2.5 (1.0)	2.5 (0.9)	2.5 (0.9)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
PAC-SYM score (points)			
Overall, mean (SD)	2.1 (0.8)	2.1 (0.7)	2.1 (0.8)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Stool symptoms, mean (SD)	2.3 (1.0)	2.4 (1.1)	2.3 (1.0)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Abdominal symptoms, mean (SD)	2.4 (1.2)	2.4 (0.8)	2.4 (1.0)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Rectal symptoms, mean (SD)	1.3 (1.2)	1.3 (0.8)	1.3 (1.0)
Missing, *n* (%)	2 (6.7)	2 (5.7)	4 (6.2)
Bowel frequency, number reported over 14 days (diary data)			
Attempts to empty bowels, mean (SD)	20.3 (10.6)	21.2 (13.2)	20.8 (12.0)
Missing, *n* (%)	6 (20.0)	6 (17.1)	12 (18.5)
Times stool was actually passed, mean (SD)	12.1 (9.5)	11.3 (9.9)	11.6 (9.6)
Missing, *n* (%)	7 (23.3)	6 (17.1)	13 (20.0)
Nature of bowel movement, number of days out of 14 (diary data)			
Laxatives used, mean (SD)	21.7 (5.8)	23.7 (5.2)	22.8 (5.6)
Missing, *n* (%)	6 (20.0)	6 (17.1)	12 (18.5)
Glycerine suppositories used, mean (SD)	26.0 (4.0)	26.5 (3.3)	26.3 (3.6)
Missing, *n* (%)	7 (23.3)	6 (17.1)	13 (20.0)
EQ-5D-5L: 'no problem' indicated, n ***(%)***			
Mobility	6 (20.0)	9 (25.7)	15 (23.1)
Missing	3 (10.0)	2 (5.7)	5 (7.7)
Self-care	4 (13.3)	4 (11.4)	8 (12.3)
Missing	3 (10.0)	2 (5.7)	5 (7.7)
Usual activities	11 (36.7)	17 (48.6)	28 (43.1)
Missing	3 (10.0)	2 (5.7)	5 (7.7)
Pain/discomfort	24 (80.0)	30 (85.7)	54 (83.1)
Missing	3 (10.0)	2 (5.7)	5 (7.7)
Anxiety/depression	15 (50.0)	20 (57.1)	35 (53.8)
Missing	3 (10.0)	2 (5.7)	5 (7.7)

TABLE 17 The CapaCiTY trial 2 outcome measure data at baseline (*continued*)

Outcome measure	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
EQ-VAS score (points)			
Total, mean (SD)	63.9 (20.3)	70.9 (19.1)	67.8 (19.8)
Missing, *n* (%)	3 (10.0)	2 (5.7)	5 (7.7)
PHQ-9 depression severity,* n *(%)			
None	2 (6.7)	2 (5.7)	4 (6.2)
Mild	14 (46.7)	16 (45.7)	30 (46.2)
Moderate	5 (16.7)	8 (22.9)	13 (20.0)
Moderately severe	3 (10.0)	2 (5.7)	5 (7.7)
Severe	6 (20.0)	7 (20.0)	13 (20.0)
Missing	2 (6.7)	2 (5.7)	4 (6.2)
GAD-7 anxiety severity,* n *(%)			
None	8 (26.7)	15 (42.9)	23 (35.4)
Mild	8 (26.7)	5 (14.3)	13 (20.0)
Moderate	6 (20.0)	9 (25.7)	15 (23.1)
Severe	3 (10.0)	1 (2.9)	4 (6.2)
Missing	3 (10.0)	3 (8.6)	6 (9.2)

TABLE 18 The CapaCiTY trial 2 primary outcome: PAC-QoL score, low-volume vs. high-volume TAI and difference in means at 3 months

Intervention	Baseline, mean (SD)	Baseline, median (IQR)	3 months, mean (SD)	3 months, median (IQR)	Difference in means (95% CI)
Low-volume TAI (*n* = 19)	2.4 (0.8)	2.4 (1.9–2.9)	2.2 (0.8)	2.0 (1.5–2.8)	Reference
High-volume TAI (*n* = 25)	2.3 (0.7)	2.4 (1.8–2.8)	1.8 (0.9)	1.8 (1.1–2.3)	–0.37 (–0.89 to 0.15)

Further evidence of the greater benefit of high-volume TAI could be inferred from the fact that 15 patients switched from low-volume to high-volume TAI but only four patients switched from high-volume to low-volume TAI and two of these six switched back again to high-volume TAI (*Table 21*).

Many of the treatment responses improved over time, suggesting a possible beneficial effect of TAI. This improvement cannot be definitively assigned to the treatment owing to confounding factors such as regression to the mean, loss of participants and the absence of a sham control. However, it is reasonable to postulate that survival rate of therapy (being both cumbersome and unpleasant) indicated ongoing patient perception that it had clinical benefit.

A secondary aim of CapaCiTY trial 2 was to observe the survival rate of TAI therapy against time, this being a surrogate of ongoing perceived patient benefit (given the invasive and time-consuming nature of self-administering the therapy). *Figure 13* shows that three-quarters of patients were still using TAI at 12 months – an impressively high number. Concomitant medicine usage was roughly equal in both groups (*Table 22*).

TABLE 19 The CapaCiTY trial 2 continuous secondary outcomes at baseline and follow-up for participants with data collected at 3, 6 and 12 months by randomised treatment group

Intervention	3 months					6 months					12 months				
	n	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, median (IQR)	Follow-up, median (IQR)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, median (IQR)	Follow-up, median (IQR)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, median (IQR)	Follow-up, median (IQR)
PAC-QoL score (points)															
Overall															
Low-volume TAI	19	2.4 (0.8)	2.2 (0.8)	2.4 (1.9–2.9)	2.0 (1.5–2.8)	19	2.4 (0.7)	1.8 (0.9)	2.4 (1.9–2.9)	1.4 (1.1–2.6)	14	2.5 (0.7)	2.1 (0.9)	2.5 (2.0–2.9)	1.9 (1.4–2.7)
High-volume TAI	25	2.3 (0.7)	1.8 (0.9)	2.4 (1.8–2.8)	1.8 (1.1–2.3)	21	2.2 (0.7)	1.4 (0.8)	2.4 (1.8–2.8)	1.2 (0.9–1.9)	18	2.3 (0.7)	1.5 (0.9)	2.3 (1.8–2.8)	1.1 (0.9–2.1)
Dissatisfaction															
Low-volume TAI	19	3.4 (0.4)	2.8 (0.7)	3.4 (3.2–3.8)	3.0 (2.2–3.4)	19	3.4 (0.4)	2.2 (0.9)	3.4 (3.2–3.6)	2.2 (1.8–2.8)	14	3.4 (0.4)	2.5 (1.0)	3.4 (3.2–3.6)	2.5 (2.0–3.2)
High-volume TAI	24	3.1 (0.7)	2.5 (0.9)	3.2 (2.8–3.6)	2.8 (2.1–3.1)	20	3.0 (0.7)	2.1 (1.1)	3.1 (2.6–3.6)	2.1 (1.3–3.0)	17	3.1 (0.7)	2.2 (1.1)	3.2 (2.8–3.6)	2.2 (1.4–2.4)
Physical discomfort															
Low-volume TAI	18	2.7 (0.9)	2.4 (0.9)	2.9 (2.3–3.3)	2.3 (2.0–3.0)	19	2.6 (0.9)	1.8 (1.0)	2.8 (2.0–3.3)	1.8 (1.0–2.8)	14	2.6 (0.9)	2.1 (1.2)	2.9 (2.3–3.3)	2.5 (1.3–2.8)
High-volume TAI	25	2.6 (0.7)	1.9 (0.9)	2.5 (2.3–3.0)	1.8 (1.3–2.3)	20	2.4 (0.6)	1.3 (0.9)	2.5 (2.1–2.8)	1.3 (0.6–2.0)	18	2.4 (0.6)	1.6 (0.9)	2.5 (2.3–2.8)	1.3 (1.0–2.0)
Psychosocial discomfort															
Low-volume TAI	19	1.6 (1.0)	1.5 (1.1)	1.5 (0.8–2.8)	1.3 (0.8–2.4)	19	1.6 (1.0)	1.3 (1.1)	1.5 (0.9–2.3)	0.9 (0.5–2.3)	14	2.0 (1.1)	1.7 (1.3)	1.9 (1.1–2.9)	1.6 (0.5–3.1)
High-volume TAI	25	1.7 (1.0)	1.2 (0.9)	1.8 (0.8–2.6)	0.9 (0.6–1.9)	21	1.5 (1.1)	0.8 (0.8)	1.3 (0.6–2.4)	0.6 (0.3–1.1)	18	1.5 (1.1)	1.0 (0.9)	1.2 (0.6–2.5)	0.6 (0.4–1.8)
Worries and concerns															
Low-volume TAI	19	2.4 (1.0)	2.3 (1.0)	2.6 (1.5–3.1)	2.2 (1.6–2.8)	19	2.4 (0.9)	1.8 (1.1)	2.6 (1.9–3.1)	1.5 (0.9–2.5)	14	2.5 (0.8)	2.0 (1.1)	2.8 (2.1–3.1)	2.0 (1.2–2.5)
High-volume TAI	25	2.4 (1.0)	1.9 (1.1)	2.4 (1.8–3.1)	1.8 (1.0–2.4)	21	2.3 (0.9)	1.4 (1.1)	2.3 (1.8–3.0)	1.0 (0.6–1.9)	18	2.4 (0.9)	1.5 (1.1)	2.2 (1.8–3.0)	1.0 (0.6–2.6)
PAC-SYM score (points)															
Overall															
Low-volume TAI	19	2.0 (0.8)	1.8 (0.8)	2.0 (1.4–2.6)	1.8 (1.2–2.1)	19	2.0 (0.8)	1.4 (0.8)	2.0 (1.4–2.4)	1.4 (0.8–1.7)	14	2.0 (0.9)	1.6 (0.8)	1.8 (1.3–2.4)	1.5 (0.8–2.3)
High-volume TAI	25	2.0 (0.7)	1.4 (0.7)	2.1 (1.4–2.5)	1.4 (1.0–1.8)	21	1.9 (0.6)	1.2 (0.6)	1.9 (1.4–2.4)	1.3 (0.7–1.7)	18	1.9 (0.6)	1.3 (0.6)	1.9 (1.4–2.4)	1.3 (0.8–1.7)
Stool symptoms															
Low-volume TAI	19	2.2 (1.0)	2.0 (1.0)	2.2 (1.6–3.0)	2.0 (1.0–2.4)	19	2.1 (1.0)	1.5 (0.9)	2.2 (1.4–3.0)	1.6 (0.8–2.0)	14	2.0 (0.8)	1.7 (0.9)	2.0 (1.4–2.4)	1.6 (1.2–2.4)
High-volume TAI	25	2.2 (1.1)	1.6 (0.8)	2.4 (1.6–3.0)	1.8 (1.2–2.0)	21	2.1 (1.1)	1.4 (0.8)	2.4 (1.4–3.0)	1.4 (0.8–2.0)	18	2.1 (1.0)	1.6 (0.9)	2.3 (1.4–3.0)	1.8 (0.8–2.4)
Abdominal symptoms															
Low-volume TAI	19	2.3 (1.2)	2.0 (0.9)	2.0 (2.0–3.5)	2.0 (1.3–2.8)	19	2.5 (1.1)	1.7 (1.0)	2.3 (2.0–3.5)	1.5 (0.8–2.3)	14	2.5 (1.2)	1.9 (1.1)	2.4 (2.0–4.0)	2.0 (0.8–2.8)
High-volume TAI	25	2.3 (0.7)	1.8 (0.9)	2.5 (1.8–2.8)	2.0 (1.3–2.3)	21	2.1 (0.7)	1.4 (0.7)	2.0 (1.8–2.8)	1.5 (1.0–2.0)	18	2.2 (0.8)	1.4 (0.8)	2.4 (1.8–2.8)	1.5 (0.8–2.3)

TABLE 19 The CapaCiTY trial 2 continuous secondary outcomes at baseline and follow-up for participants with data collected at 3, 6 and 12 months by randomised treatment group (*continued*)

Intervention	3 months					6 months					12 months				
	n	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, median (IQR)	Follow-up, median (IQR)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, median (IQR)	Follow-up, median (IQR)	*n*	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, median (IQR)	Follow-up, median (IQR)
Rectal symptoms															
Low-volume TAI	19	1.1 (1.1)	1.0 (1.3)	1.0 (0.3–1.7)	0.3 (0.3–1.7)	19	1.1 (1.0)	0.8 (0.8)	1.0 (0.3–1.7)	1.0 (0.0–1.3)	14	1.2 (1.1)	1.0 (1.1)	0.8 (0.3–1.7)	0.7 (0.3–1.3)
High-volume TAI	25	1.1 (0.7)	0.6 (0.7)	1.0 (0.7–1.7)	0.3 (0.0–1.0)	21	1.0 (0.7)	0.5 (0.6)	1.0 (0.3–1.3)	0.3 (0.0–1.0)	18	1.1 (0.7)	0.8 (0.9)	1.2 (0.3–1.7)	0.3 (0.0–1.3)
Irrigation journal															
Average number of times per week that the patient has used their anal irrigation															
Low-volume TAI	19	–	5.2 (7.5)	–	4.0 (1.0–7.0)	19	–	3.3 (2.5)	–	3.0 (2.0–6.0)	17	–	2.3 (2.1)	–	2.0 (1.0–3.0)
High-volume TAI	21	–	3.1 (2.1)	–	3.0 (2.0–4.0)	22	–	2.8 (2.5)	–	3.0 (0.0–4.0)	19	–	2.6 (2.1)	–	3.0 (0.0–4.0)
Average volume (ml) of water used per irrigation[a]															
Low-volume TAI	16	–	147.8 (94.2)	–	143.5 (70.0–210.0)	13	–	97.8 (92.6)	–	70.0 (0.0–170.0)	11	–	83.2 (102.9)	–	70.0 (0.0–210.0)
High-volume TAI	26	–	579.8 (296.0)	–	570.0 (400.0–750.0)	32	–	518.3 (316.4)	–	500.0 (376.5–745.0)	25	–	535.7 (381.7)	–	500.0 (373.0–703.0)
Diary data															
Bowel frequency: mean number of attempts to empty bowels over 2 weeks															
Low-volume TAI	19	19.7 (11.3)	17.3 (10.6)	18.0 (11.0–28.0)	20.0 (7.0–23.0)	15	18.1 (8.3)	19.5 (22.6)	18.0 (11.0–22.0)	11.0 (10.0–22.0)	12	21.8 (12.2)	19.2 (13.7)	20.5 (12.0–30.0)	17.5 (10.5–23.0)
High-volume TAI	18	23.1 (14.1)	19.3 (9.8)	21.5 (13.0–33.0)	16.5 (12.0–26.0)	17	25.0 (13.8)	16.6 (9.1)	23.0 (17.0–34.0)	16.0 (10.0–22.0)	13	24.1 (16.5)	18.4 (12.8)	20.0 (13.0–37.0)	13.0 (7.0–25.0)
Bowel frequency: mean number of times stool was passed over 2 weeks															
Low-volume TAI	18	11.8 (10.2)	10.9 (6.9)	9.5 (5.0–15.0)	10.0 (7.0–13.0)	16	8.8 (5.3)	12.8 (13.9)	8.0 (4.5–13.0)	9.5 (6.0–15.0)	13	12.2 (11.6)	11.2 (8.7)	9.0 (5.0–13.0)	10.0 (5.0–15.0)
High-volume TAI	18	13.1 (11.2)	13.3 (8.2)	10.0 (6.0–17.0)	11.5 (8.0–16.0)	17	14.2 (11.0)	11.7 (5.3)	11.0 (7.0–17.0)	9.0 (8.0–15.0)	13	12.2 (12.6)	12.5 (9.0)	10.0 (4.0–15.0)	9.0 (7.0–18.0)
Nature of bowel movement: mean number of days (out of 14) laxatives used															
Low-volume TAI	19	21.7 (6.2)	22.7 (5.5)	23.0 (14.0–28.0)	25.0 (17.0–28.0)	16	22.4 (5.7)	22.4 (5.5)	24.0 (16.5–28.0)	23.0 (18.5–28.0)	13	20.8 (6.0)	22.8 (6.5)	23.0 (14.0–26.0)	25.0 (20.0–28.0)
High-volume TAI	18	22.7 (5.6)	23.1 (5.7)	25.0 (17.0–28.0)	26.0 (20.0–28.0)	17	24.1 (5.2)	23.4 (6.0)	27.0 (22.0–28.0)	27.0 (17.0–28.0)	13	22.0 (6.0)	24.4 (5.7)	23.0 (16.0–28.0)	28.0 (23.0–28.0)

continued

TABLE 19 The CapaCiTY trial 2 continuous secondary outcomes at baseline and follow-up for participants with data collected at 3, 6 and 12 months by randomised treatment group (*continued*)

	3 months					6 months					12 months				
Intervention	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Baseline, median (IQR)**	**Follow-up, median (IQR)**	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Baseline, median (IQR)**	**Follow-up, median (IQR)**	***n***	**Baseline, mean (SD)**	**Follow-up, mean (SD)**	**Baseline, median (IQR)**	**Follow-up, median (IQR)**
Nature of bowel movement: mean number of days (out of 14) glycerine suppositories used															
Low-volume TAI	18	26.5 (3.5)	26.7 (3.7)	28.0 (27.0–28.0)	28.0 (28.0–28.0)	15	26.7 (3.6)	27.5 (1.4)	28.0 (27.0–28.0)	28.0 (28.0–28.0)	12	26.3 (4.2)	26.1 (5.3)	28.0 (27.5–28.0)	28.0 (28.0–28.0)
High-volume TAI	18	26.6 (2.7)	26.8 (3.3)	28.0 (26.0–28.0)	28.0 (27.0–28.0)	17	25.6 (4.1)	27.4 (1.5)	28.0 (24.0–28.0)	28.0 (28.0–28.0)	13	26.7 (2.9)	27.6 (1.0)	28.0 (27.0–28.0)	28.0 (28.0–28.0)
EQ-VAS score (points)															
Low-volume TAI	19	60.8 (22.7)	56.1 (26.0)	65.0 (45.0–75.0)	60.0 (40.0–75.0)	18	61.1 (21.2)	63.3 (22.4)	67.5 (50.0–75.0)	68.5 (60.0–80.0)	13	62.7 (21.9)	49.6 (19.6)	70.0 (60.0–75.0)	50.0 (40.0–64.0)
High-volume TAI	25	72.5 (19.0)	70.0 (25.9)	80.0 (65.0–90.0)	80.0 (62.0–90.0)	21	69.7 (19.2)	67.7 (22.4)	80.0 (50.0–80.0)	70.0 (49.0–85.0)	17	67.2 (20.4)	69.2 (22.1)	70.0 (50.0–80.0)	80.0 (50.0–85.0)
PHQ-9 score (points)															
Low-volume TAI	19	9.7 (7.1)	9.1 (6.9)	10.0 (3.0–17.0)	6.0 (4.0–15.0)	19	9.4 (7.0)	9.3 (7.6)	8.0 (3.0–17.0)	5.0 (4.0–11.0)	14	9.6 (8.3)	11.4 (8.5)	6.5 (3.0–17.0)	9.5 (4.0–21.0)
High-volume TAI	24	6.6 (6.4)	8.1 (8.1)	5.0 (1.5–11.0)	4.0 (1.0–17.0)	21	6.0 (5.8)	6.6 (6.8)	3.0 (2.0–10.0)	4.0 (1.0–9.0)	18	6.4 (5.7)	7.1 (6.7)	5.0 (2.0–10.0)	6.0 (2.0–10.0)
GAD-7 score (points)															
Low-volume TAI	19	7.8 (6.5)	6.9 (6.5)	6.0 (3.0–13.0)	6.0 (2.0–12.0)	19	7.6 (6.4)	7.4 (6.2)	5.0 (3.0–13.0)	7.0 (3.0–9.0)	14	7.7 (7.5)	9.9 (8.1)	4.5 (1.0–13.0)	9.0 (3.0–18.0)
High-volume TAI	24	6.0 (5.8)	6.9 (6.9)	4.0 (2.0–8.0)	4.0 (1.0–13.1)	21	4.8 (4.3)	5.9 (6.7)	4.0 (2.0–6.0)	4.0 (0.0–12.0)	18	4.9 (4.5)	6.6 (7.4)	4.0 (2.0–6.0)	3.5 (0.0–14.0)
Global patient satisfaction score (points)															
Low-volume TAI	19	–	2.0 (1.2)	–	2.0 (1.0–3.0)	19	–	2.5 (1.0)	–	3.0 (2.0–3.0)	14	–	2.0 (1.2)	–	2.0 (2.0–3.0)
High-volume TAI	24	–	2.6 (1.1)	–	2.5 (2.0–3.5)	21	–	2.9 (0.9)	–	3.0 (3.0–3.0)	18	–	2.8 (0.9)	–	3.0 (3.0–3.0)
Global patient improvement score (points)															
Low-volume TAI	19	–	40.4 (31.0)	–	40.0 (11.0–70.0)	19	–	51.7 (30.1)	–	56.0 (20.0–80.0)	14	–	46.4 (31.2)	–	50.0 (20.0–70.0)
High-volume TAI	25	–	53.6 (28.7)	–	60.0 (35.0–70.0)	21	–	70.2 (25.7)	–	80.0 (70.0–85.0)	18	–	66.1 (24.6)	–	75.0 (65.0–80.0)

a Data for this outcome was collected by treatment used and not treatment assigned.

Note
The results under each time point summarise only the data from participants with recorded outcomes at both baseline and that follow-up time point.

TABLE 20 The CapaCiTY trial 2 binary secondary outcomes (EQ-5D-5L score) at baseline and follow-up for patients with data collected at 3, 6 and 12 months by randomised treatment group

	3 months			6 months			12 months		
Intervention	*N*	Indicating problems at baseline, *n* (%)	Indicating problems at follow-up, *n* (%)	*N*	Indicating problems at baseline, *n* (%)	Indicating problems at follow-up, *n* (%)	*N*	Indicating problems at baseline, *n* (%)	Indicating problems at follow-up, *n* (%)
Mobility									
Low-volume TAI	19	3 (15.8)	4 (21.1)	18	3 (16.7)	4 (22.2)	13	4 (30.8)	3 (23.1)
High-volume TAI	25	8 (32.0)	6 (24.0)	21	7 (33.3)	6 (28.6)	17	6 (35.3)	4 (23.5)
Self-care									
Low-volume TAI	19	4 (21.1)	2 (10.5)	18	3 (16.7)	3 (16.7)	13	3 (23.1)	2 (15.4)
High-volume TAI	25	4 (16.0)	3 (12.0)	21	4 (19.0)	5 (23.8)	17	4 (23.5)	4 (23.5)
Usual activities									
Low-volume TAI	19	9 (47.4)	7 (36.8)	18	8 (44.4)	6 (33.3)	13	8 (61.5)	8 (61.5)
High-volume TAI	25	12 (48.0)	9 (36.0)	21	10 (47.6)	7 (33.3)	17	7 (41.2)	6 (35.3)
Pain/discomfort									
Low-volume TAI	19	16 (84.2)	19 (100.0)	18	15 (83.3)	14 (77.8)	13	11 (84.6)	10 (76.9)
High-volume TAI	25	22 (88.0)	18 (72.0)	21	18 (85.7)	13 (61.9)	17	14 (82.4)	10 (58.8)
Anxiety/depression									
Low-volume TAI	19	12 (63.2)	12 (63.2)	18	11 (61.1)	10 (55.6)	13	6 (46.2)	11 (84.6)
High-volume TAI	24	13 (54.2)	13 (54.2)	21	11 (52.4)	10 (47.6)	17	9 (52.9)	9 (52.9)

Note
The results under each time point summarise only the data from participants with recorded outcomes at both baseline and that follow-up time point.

TABLE 21 Crossover and withdrawal summaries for any patient who changed or stopped treatment during the trial

Characteristic, *n*	Assigned to low-volume TAI (*N* = 30)	Assigned to high-volume TAI (*N* = 35)	Total (*N* = 65)
Number of patients who switched from low-volume to high-volume TAI	15	0	15
Number of patients who switched from high-volume to low-volume TAI	4[a]	4	8
Number of patients who discontinued therapy	4	11	15
Numbers of patients who switched and/or discontinued therapy	17	12	29
Reason for withdrawal			
Sensation of incomplete evacuation	1	3	4
Frequent trips to the toilet	0	2	2
Satisfactory defaecation achieved with very low volumes (< 300 ml)	0	1	1
No significant effect on symptoms or QoL	2	5	7
Treatment not acceptable to patient	0	1	1

continued

TABLE 21 Crossover and withdrawal summaries for any patient who changed or stopped treatment during the trial (*continued*)

Characteristic, *n*	Assigned to low-volume TAI (*N* = 30)	Assigned to high-volume TAI (*N* = 35)	Total (*N* = 65)
Excess bloating	0	1	1
Excess pain	0	3	3
Other AE	0	1	1
Other reason	1	1	2
Total	4	18	22

a Four patients switched from high-volume to low-volume TAI and then back again.

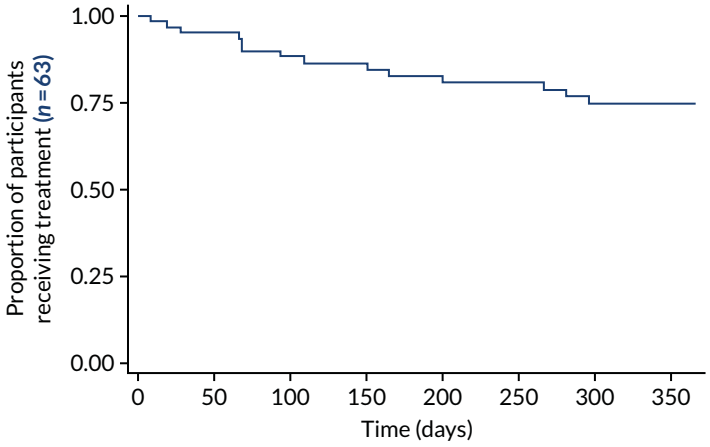

FIGURE 13 Survival rate of TAI therapy: Kaplan–Meier plot for time to cessation of treatment (all participants).

TABLE 22 Use of concomitant medication

Characteristic (*n*)	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
Number of patients reporting the use of concomitant medications	28	28	56
Number of concomitant medications reported	171	156	327

Safety analyses

The anal irrigation systems used in CapaCiTY trial 2 are widespread and established in clinical use throughout the NHS, with known AEs (22%) being mostly low grade and reversible. All trial interventions were as per the standard care provided in the NHS for CC. Related AEs and SAEs were recorded on the CRF and in the medical notes to enable assessment and reporting in line with sponsor and regulatory requirements. Causality was at the discretion of the health-care provider (e.g. research nurse, physiotherapist, principal investigator, delegated member of team).

Serious adverse events that were considered 'related' and 'unexpected' were reported to the sponsor within 24 hours of learning of the event and to the main REC within 15 days, in line with the required time frame. The number of patients reporting AEs/SAEs was presented by trial group.

The study (not being of a medicinal product) did not record unrelated AEs. SAEs and related AEs were small in number, with six SAEs reported (*Table 23*). None of these was related to trial treatment and all were resolved.

Results: cost-effectiveness

Summary and completeness of data

Participants were allocated randomly to low-volume or high-volume TAI. Variables used to estimate costs and QALYs are described in *Table 24*. The average training time for the two methods was similar. Participants were instructed to make daily use of their allocated method for the first 14 days, reducing to alternate days depending on response. Estimated use of TAI was similar in the two groups during the first month, but thereafter a difference emerged. Average daily use in the high-volume group diminished over time, due primarily to the number of users diminishing, and there was very little crossover to low-volume TAI. There was a similar decrease in low-volume TAI use but substantial crossover to high-volume TAI over the duration of follow-up. The cost of TAI was the predominant determinant of overall cost in each period. TAI treatment was provided as a prescription and the baseline analysis estimated the number of prescriptions of TAI equipment received (see *Table 24*). Levels of use of (non-irrigation) prescription drugs and community health-care were relatively low and similar comparing groups. Hence, cost differences were driven by the intervention costs. Societal costs reflected a minority ($\approx$ 20%) of patients reporting substantial time away from work. Reported days away from work in the periods 4–6 and 7–12 months suggest more return to work in the high-volume group, contributing to a lower societal cost, although the cost difference is not statistically significant ($p = 0.34$). Completeness of cost data diminishes as follow-up progresses from 86% in the first period to 48% in the last period. Comparing QoL scores, there is an apparent trend of improving QoL in the high-volume TAI group not apparent in the low-volume TAI group, although this may be confounded by increasing missingness of data. Again, completeness of EQ-5D-5L data decreases as follow-up proceeds, from 94% to 62%.

Cost-effectiveness analyses

The base-case model is reported in *Table 25*. Compared with low-volume TAI, high-volume TAI featured similar costs (median difference −£8, 95% CI −£240 to £221) and significantly higher QoL (0.093 QALYs, 95% CI 0.016 to 0.175 QALYs); these findings are visualised in *Figure 14*. Incremental NMB values are positive across the commonly used range of WTP thresholds, indicating that high-volume TAI is cost-effective and appears to deliver a gain to the health system compared with alternative choices. These findings are presented as a CEAC showing the probability of being cost-effective at varying WTP thresholds. At the NICE-recommended WTP threshold of £30,000 per QALY, the probability that high-volume TAI is a cost-effective alternative to low-volume TAI is 99%. The EVPI (per subject) reflects the opportunity loss of ongoing uncertainty. At a WTP threshold of £30,000 per QALY, EVPI per subject is just £2, reflecting the certainty of the finding. Assuming that the finding is robust, this would indicate that further research is not merited.

The complete-case analysis is also presented (see *Table 26*). Although numbers contributing are small, the findings are similar to the base case, if less precise. The base-case analysis costed the number of irrigation prescriptions received by each participant, assuming that unused portions of prescriptions were lost. As a sensitivity analysis the number of daily uses was costed to provide greater granularity to the costing. This marginally increased the incremental costs, but the overall finding remained robust. Given the small numbers of participants in the trial, as a second sensitivity analysis the base-case model was re-estimated as a univariate regression (NMB at varying WTP thresholds) to explore distributional assumptions. Qualitatively, the finding was similar, although at a WTP threshold of £30,000 per QALY the probability that high-volume TAI is cost-effective reduced to 91%.

TABLE 23 The CapaCiTY trial 2 related AEs and SAEs

Characteristic (*n*)	Low-volume TAI (*N* = 30)	High-volume TAI (*N* = 35)	Total (*N* = 65)
Related AEs			
Number of patients reporting AE	11	5	16
Number of AEs reported			
Abdominal cramping	1	0	1
Abdominal pain	3	3	6
Anal/rectal pain or discomfort	17	9	26
Constipation	1	0	1
Loose motions	1	0	1
Pain	1	4	5
Rectal bleeding	10	12	22
Miscellaneous	2	4	6
Severity			
Mild	22	18	40
Moderate	8	12	20
Severe	4	2	6
Life-threatening	2	0	2
Action			
No action taken	23	22	45
Withdrawal	0	3	3
Concomitant medication	5	5	10
Non-drug therapy	6	2	8
SAE, *n*			
Number of patients reporting SAE	6	0	6
Number of SAEs reported			
Life-threatening, unlikely to be related			
Life-threatening, related			
Required hospitalisation or prolongation of existing hospitalisation, unlikely to be related	6	0	6
Required hospitalisation or prolongation of existing hospitalisation, related			
Expectedness			
Expected	3	0	3
Unexpected	3	0	3
Action taken			
No action taken	1	0	1
Non-drug therapy	1	0	1
Hospitalisation	4	0	4

TABLE 24 The CapaCiTY trial 2 economic analysis variables (£, 2018)

Characteristic	Low-volume TAI (*N* = 30)			High-volume TAI (*N* = 35)		
	Mean	SD	*n*	Mean	SD	*n*
Resource use						
0–1 months						
Training time, hours	1.53	0.51	29	1.60	0.46	34
Low-volume TAI, days	21.90	0.00	24	0.00	0.00	32
High-volume TAI, days	0.00	0.00	30	19.29	6.70	35
Number of prescriptions	1.85	1.83	26	1.19	1.20	32
1–3 months						
Low-volume TAI, days	22.23	14.41	21	0.00	0.00	26
High-volume TAI, days	3.54	9.17	30	14.30	12.86	35
Number of prescriptions	0.91	1.11	22	0.96	0.93	23
GP visits	0.05	0.22	21	0.00	0.00	22
District nurse visits	0.00	0.00	21	0.00	0.00	22
Pharmacist visits	0.05	0.22	21	0.50	1.47	22
A&E visits	0.19	0.68	21	0.00	0.00	22
Outpatient visits	0.05	0.22	21	0.18	0.39	22
Days from work	3.52	9.87	21	4.59	21.09	22
Inpatient visits	0.00	0.00	20	0.00	0.00	22
4–6 months						
Low-volume TAI, days	16.82	20.88	22	0.33	1.60	32
High-volume TAI, days	12.87	17.24	30	15.28	17.90	35
Number of prescriptions	1.36	2.48	22	0.71	1.30	24
GP visits	0.05	0.22	20	0.04	0.21	23
District nurse visits	0.00	0.00	20	0.00	0.00	23
Pharmacist visits	0.40	1.19	20	0.00	0.00	23
A&E visits	0.05	0.22	20	0.04	0.21	23
Outpatient visits	0.55	0.60	20	0.17	0.39	23
Days from work	8.20	21.47	20	0.68	2.01	22
Inpatient visits	0.15	0.67	20	0.00	0.00	22
7–12 months						
Low-volume TAI, days	10.50	22.50	20	1.84	10.55	33
High-volume TAI, days	16.23	29.92	30	22.20	31.84	35
Number of prescriptions	0.62	1.07	21	0.65	1.11	23
GP visits	0.29	0.69	17	0.05	0.23	19
District nurse visits	0.00	0.00	17	0.00	0.00	19
Pharmacist visits	0.06	0.24	17	0.05	0.23	19
A&E visits	0.00	0.00	17	0.00	0.00	19
Outpatient visits	0.24	0.44	17	0.26	0.65	19
Days from work	7.24	23.93	17	1.16	4.00	19
Inpatient visits	0.00	0.00	17	0.00	0.00	18

continued

TABLE 24 The CapaCiTY trial 2 economic analysis variables (£, 2018) (*continued*)

Characteristic	Low-volume TAI (*N* = 30)			High-volume TAI (*N* = 35)		
	Mean	SD	*n*	Mean	SD	*n*
NHS cost (£)						
Treatment period (0–1 months)	370	110	24	462	69	32
1–3 months	294	132	18	284	152	21
4–6 months	525	340	19	435	277	20
7–12 months	556	359	14	565	305	17
Overall	1995	796	10	1816	629	15
Societal cost (£)						
Overall	4985	6425	10	2803	3246	14
EQ-5D-5L						
Baseline (0 months)	0.64	0.28	27	0.63	0.29	34
3 months	0.68	0.24	24	0.73	0.26	29
6 months	0.58	0.31	20	0.70	0.31	24
12 months	0.65	0.35	19	0.74	0.23	21
QALYs						
0–12 months	0.62	0.37	10	0.72	0.26	15

Notes
Subtotals may not sum to totals because of different numbers of participants contributing.
Days from work included in societal cost but not in NHS cost.
Number of prescriptions includes all non-irrigation prescribed medication.

TABLE 25 The CapaCiTY trial 2 cost-effectiveness analysis (£, 2018)

High-volume vs. low-volume TAI	ICER (95% CI)	IC (95% CI)	IQ (95% CI)	CEAC *p*-value[a]	CEAC *p*-value[b]	NMB[a] (95% CI)	NMB[b] (95% CI)	EVPI[b]
Base case	[c] ([c] to 3409)	−8 (−240 to 221)	0.093 (0.016 to 0.175)	0.993	0.993	1399 (266 to 2648)	2781 (523 to 5252)	2
Complete case	[c] ([c] to 4837)	−335 (−907 to 313)	0.087 (−0.082 to 0.264)	0.907	0.887	1643 (−888 to 4428)	2947 (−2091 to 8365)	160
Sensitivity analysis 1[d]	910 ([c] to 7119)	83 (−120 to 255)	0.091 (0.01 to 0.179)	0.983	0.985	1277 (105 to 2600)	2651 (276 to 5281)	6
Sensitivity analysis 2[e]	–	–	–	0.881	0.907	2097 (−1387 to 5543)	2378 (−1049 to 5988)	73

a Probability cost-effective at WTP threshold of £15,000 per QALY.
b Probability cost-effective at WTP threshold of £30,000 per QALY.
c Denotes a dominant strategy: negative change in cost and positive change in QALYs.
d Irrigation cost per use.
e Univariate regression (NMB) of base case.

Notes
Bootstrapped 95% CIs; median ICERs.
Base-case and sensitivity analyses: imputed with 50 draws; assuming MAR.
Complete case: includes only participants with complete cost and QALY data; assuming missing completely at random.

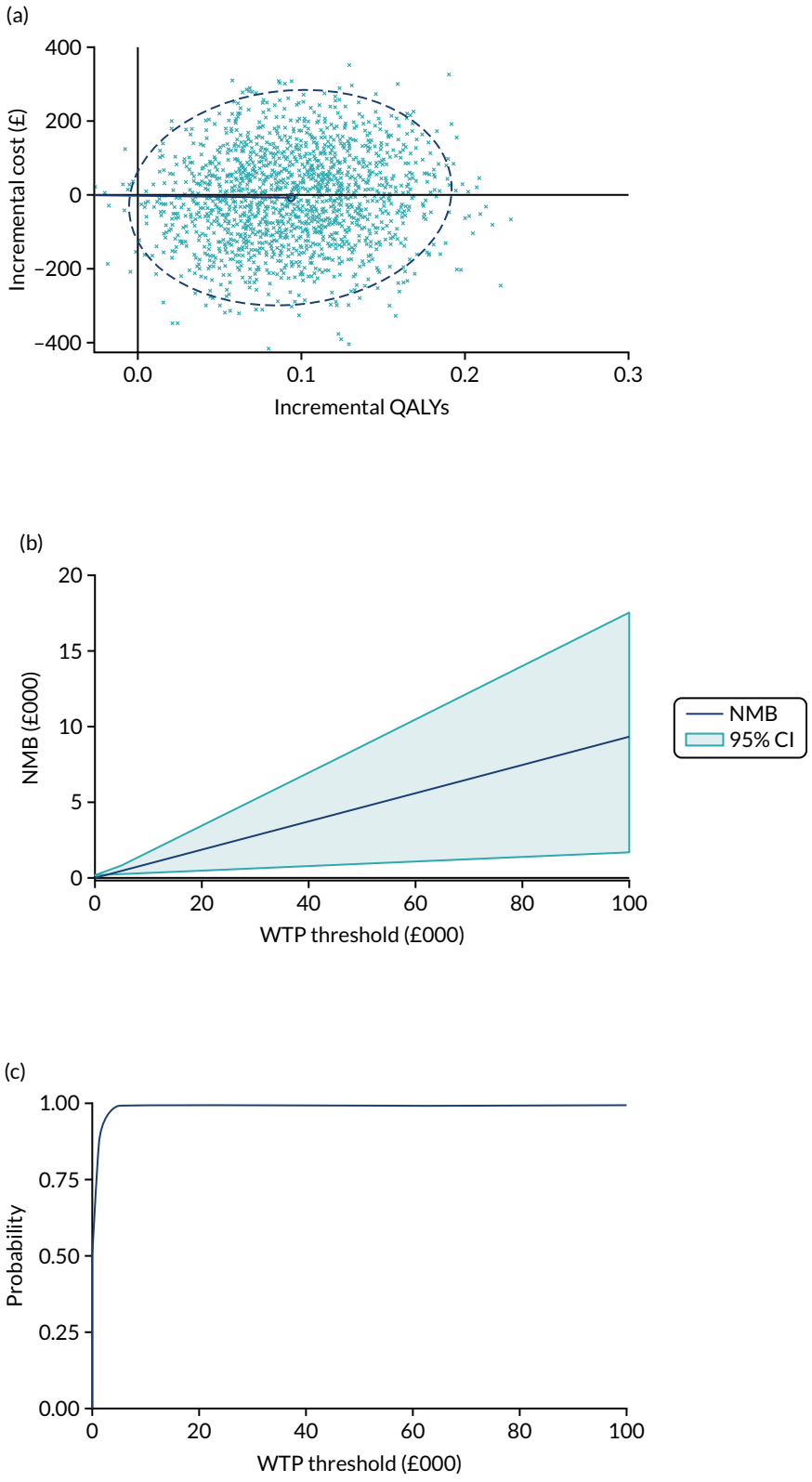

FIGURE 14 The CapaCiTY trial 2 cost-effectiveness analysis: base case. (a) ICER plane [the credible region (dashed circle) shows where 95% of estimates lie]; (b) incremental NMB; (c) CEAC; and (d) EVPI. (*continued*)

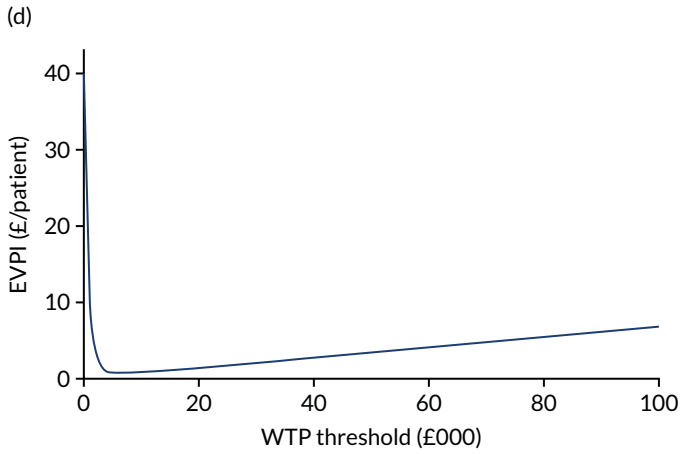

FIGURE 14 The CapaCiTY trial 2 cost-effectiveness analysis: base case. (a) ICER plane [the credible region (dashed circle) shows where 95% of estimates lie]; (b) incremental NMB; (c) CEAC; and (d) EVPI.

Results

Patient experience and qualitative analysis

Emergent themes are presented in this section. Numbers in square brackets refer to the numbered quotations in *Appendix 2, Quotations from participants contributing to qualitative analysis in all three trials, CapaCiTY trial 2: transanal irrigation*.

Rapport with nurse

Several patients mentioned the importance of the positive rapport that they had with the TAI nurse. Staff echoed the importance of rapport and also indicated that demonstrating enthusiasm and belief in the TAI system appeared to assist patients [1].

Transanal irrigation training

Patients recalled the TAI training as a positive experience and particularly liked that they had the option to try the device either in clinic (for the first time) with the nurse close to hand or at home on their own [2]. Patients also found the telephone follow-up support reassuring [3, 4]. Staff noted the importance of these follow-up support telephone calls and how they helped instil confidence in the patients.

Although the information about how to use the TAI system was clear, for some patients it was still a lot of information to take in at once [5]. Therefore, the follow-up telephone calls allowed patients to troubleshoot with the TAI nurse. Staff and patients both felt that the follow-up timings seemed appropriate. For some patients it took a little getting used to the device [6]. However, several found both high-volume and low-volume TAI devices relatively easy to use [7].

Initial expectations of transanal irrigation compared with actual experience

A number of patients spoke about their initial fears about whether or not TAI would be painful, and several found that the device was more comfortable and easier to use than they initially thought. For a few, the TAI system could be uncomfortable, particularly at the beginning [8].

Patient views on randomisation group

Patients views about which group they were randomised to varied. For some, because they had struggled with constipation for years they wanted to have what they considered to be the most effective intervention (i.e. high-volume TAI). Others, particularly if they had a fear of TAI being painful, were pleased to have been in the low-volume TAI group [9]. However, initial trepidation often transformed after discussing the situation with their nurse.

Practical experiences of using transanal irrigation

The time taken to use the TAI device ranged from 10 minutes with the low-volume device to 20–30 minutes with the high-volume device. Patients reported using the TAI systems from once per week to several times per week. Many appeared to have a relatively easy time obtaining the devices.

Some people found TAI relatively easy to fit into their daily routine [10], whereas for others it was more difficult to factor into daily living [11]. A few patients noticed an improvement in their symptoms immediately on using TAI, whereas for others the process took longer (up to a few months) to see results [12]. Some (particularly in the high-volume TAI group) needed to get to grips with the technical elements of using the device before they started to see results.

Impact of transanal irrigation on quality of life

Several patients chose to continue using their TAI device and have found it to be of great benefit in terms of improving their overall health, mood and activity levels [13, 14]. They noted the psychological impact of not having to worry about when they use the toilet, as they now have more control over their bowels through using the TAI device. This means that they are able to plan their days more than they could prior to TAI use. Some patients have noticed that if they did not use the device their constipation symptoms began to return. Some stated that, because of their continued use of TAI, they no longer considered themselves chronically constipated [15]. Others mentioned that, although they did not feel that their bowels were 'normal', the TAI device had brought them back to their own sense of 'normal'. Irrigating daily allowed them to remove a little stool each day, relieving many of the debilitating effects of CC.

For many, the freedom from the ongoing discomfort of CC was the best thing about using the TAI system. Many stated that they would recommend TAI to someone experiencing CC. Some specifically stated that TAI was preferrable to laxatives because of the side effects from these medicines (e.g. bloating, uncontrolled bowels). A few had concerns about their ability to use the device in their later years, whereas others were happy to continue use it indefinitely.

Frustrations with transanal irrigation

Although the devices appeared to work for the most part, there were occasions when TAI was not as effective, which was frustrating for some. Many patients described that, at times, using the device felt like a bit of a chore, but ultimately a chore worth doing because of the beneficial effects. Some indicated that the most difficult part of the treatment was leakage [16]. For others the most difficult part was finding a routine that worked for them.

One patient with no success with low-volume TAI switched to high-volume TAU. The high-volume TAI system did not appear to relieve another patient's symptoms and she chose to discontinue usage.

Suggestions from patients

Suggestions included:

- additional pages in the booklet to fill in thoughts and experiences of usage
- putting the kit together themselves at clinic
- having the same sex as the intervention nurse.

Staff experience of delivering the intervention

Intervention staff found TAI intervention delivery relatively easy because they typically provided similar TAI support in their clinic. However, they also noted that they needed to be mindful of the way that they delivered even the most seemingly straightforward information because assumptions and miscommunication could contribute towards patients misusing the devices.

Some nurses indicated that they believed that the low-volume TAI is easier for patients to learn and usually quicker to use, but for this particular patient group it may be less effective. By contrast, the high-volume system may seem more onerous, with more steps to learn, and may require perseverance, but is usually more effective for this patient cohort [17].

For nurses, the most satisfying element of the intervention was when it benefited the patient. Likewise, it was frustrating when nurses felt restricted to the research protocol.

These views highlight the clash between clinical agendas (to manage patient concerns with the most suitable treatment) and research agendas (to test which treatments are most effective through randomisation, which may not always be in the best interest of the individual patient).

Staff were often under the impression that high-volume TAI was the most appropriate and most effective treatment for patients.

It was particularly difficult to convince patients who were allocated to low-volume TAI to 'stick with' a treatment that nurses believed would not work. Specifically, it was difficult to persuade frustrated patients with a long history of constipation to maintain an intervention that was not currently providing benefits. However, a few nurses did indicate that it may have been helpful to start some patients on low-volume TAI first, because the kit is somewhat easier to use, and then graduate patients up to high-volume TAI after their confidence has increased.

At times participants were removed from the study in the best interest of the patient (e.g. if interventions were not working). Furthermore, at times patients and/or staff did not believe that they could delay treatment any longer, which affected recruitment rates.

CapaCiTY trial 3: stepped-wedge randomised trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation

Intervention

Participants attended for surgery at their allocated time, with admissions procedures as per routine clinical care with normal preparation, for example bowel cleansing.

Surgical procedure

Perioperative care used normal adjuncts [including informed NHS consent, World Health Organization surgical checklists, appropriate broad-spectrum antibiotic prophylaxis, venous thromboembolism prevention, patient warming and urinary catheter insertion]. Surgery could be performed as a day case procedure in an enhanced recovery programme, although most patients had an overnight stay. Consent included discussion of the risks of conversion to open surgery and specific complications. A phosphate enema or similar (optional) could be used to clear the rectum.

Figure 15 illustrates lapVMR surgical technique. Exact surgical technique was surgeon specific (i.e. based on individual preference) but in accord with expert guidance and training. All participating surgeons required sign-off by a delegated surgical team provided by the Pelvic Floor Society, an affiliate of the Association of Coloproctology of Great Britain and Ireland. Where required, preceptorship was provided to meet sign-off requirements.

In brief, after positioning the patient (in a modified lithotomy position on a non-slip mat) and port site insertion (using standard equipment and technique), the rectosigmoid junction is retracted to the left and a peritoneal incision is made over the right side of the sacral promontory and extended in an inverted J form along the rectum and over the deepest part of the pouch of Douglas. Special care is

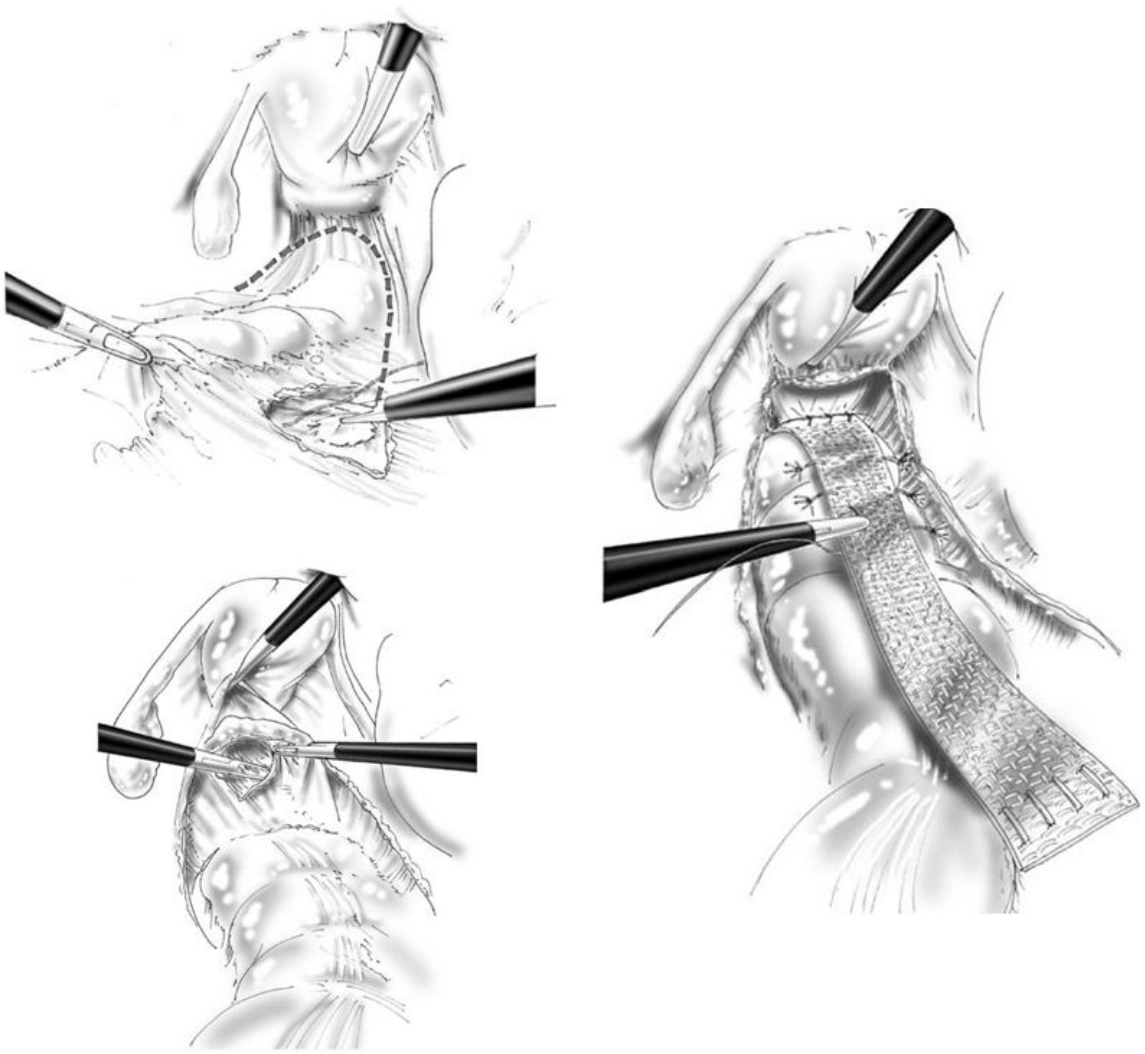

FIGURE 15 Laparoscopic ventral mesh rectopexy surgical technique. Reprinted by permission from Springer Nature: *Surgical Endoscopy*, Laparoscopic ventral recto(colpo)pexy for rectal prolapse: surgical technique and outcome for 109 patients, D'Hoore *et al.*[144] © 2006.

taken not to damage the right hypogastric nerve. Denonvillier's fascia is incised and the rectovaginal septum is broadly opened. Limited rectal mobilisation and lateral dissection are performed as required to expose the distal rectum and pelvic floor. A strip of trimmed mesh (biologic or synthetic) is inserted. Using slowly absorbable sutures (polydioxanone recommended), the mesh is sutured to the ventral aspect of the distal rectum and further fixed to the lateral seromuscular borders of the rectum proximal and distal to the incised pouch of Douglas and/or pelvic floor. The proximal end of the mesh is fixed on the sacral promontory using either sutures or an endofascia stapler. Limited traction is exerted on the rectum as required to obliterate the intussusception and/or rectocele. If deemed necessary, the posterior vaginal fornix may be elevated and sutured to the anterior aspect of the mesh; this allows closure of the rectovaginal septum and correction of a mid-compartment prolapse, if present. The lateral borders of the incised peritoneum are then closed over the mesh. This elevates the new pouch of Douglas over the colpopexy and completely covers the mesh with peritoneum. No drain is usually required. Ports should be closed directly [using an Endoclose™ device (Medtronic Ltd, Watford, UK) for lateral ports] owing to the high risk of early and late port site hernias in this group of patients with potential connective tissue laxity.

Postoperative management

Postoperative management was as per routine clinical care, usually an overnight hospital stay followed by urinary catheter removal, mobilisation and discharge. Postoperative laxative use was standardised to a weaning course of Movicol (Macrogol, Norgine) or Laxido (Macrogol, Galen) three times per day immediately postoperatively for 1 day, then reduced according to ease of bowel movements. This prevented postoperative constipation from immobility, narcotics or general anaesthesia, which if left untreated may cause painful straining on the mesh and thus protraction of the sacral promontory periosteum, potentially leading to readmission. Surgeons aimed to discharge patients 1 day postoperatively. However, length of stay was determined by clinical evaluation and could be longer if required.

Laparoscopic ventral mesh rectopexy 30-day follow-up

At 30 days, clinical recurrence of rectal prolapse was determined based on physical examination. Morbidity and mortality data were collected and treatment administered for any complications arising from lapVMR surgery. The 30-day readmission rates were also recorded. A CRF was used to capture intra-operative and postoperative data for surgery-specific outcomes.

Surgical quality assessment

Monitoring and quality control were conducted remotely via video submission and assessed against the standardised lapVMR protocol and defined assessment criteria. Monitoring took the form of planned, random and triggered sessions.

Potential principal investigators had to record and submit two unedited and anonymised videos of lapVMR performed in non-study patients. Each video was allocated to two peer reviewers of a three-member expert panel. Based on blinded assessment of unedited and anonymised videos by expert review, the panel then decided whether or not the principal investigator was 'adherent' to the standardised technique. Any disagreement was resolved by consensus after consulting a third independent expert. If deemed 'non-adherent' to the standardised technique, the site was notified that a step needed to be corrected and invited to submit another video for similar review. An unedited video of the first patient at each site enrolled in CapaCiTY trial 3 was also reviewed in this manner. Any 'failure' to comply with the standardised surgical technique for lapVMR in any submitted video of a study patient would trigger the request for a further submission of the next recruited patient from that centre. A second judgement of 'non-adherence' to the standardised technique would trigger an onsite training and monitoring session for the site. Monitoring would continue until adherence was achieved. A third 'non-adherence' or 'failure' would result in withdrawal of the site/principal investigator from the trial.

Random monitoring

All principal investigators had to record and submit the unedited and anonymised video of the lapVMR performed in a randomly selected patient enrolled in CapaCiTY trial 3 (one in five at site level). The adherence to the standardised technique was established by consensus as described for the planned monitoring.

Triggered monitoring

The DMC reviewed the morbidity and mortality rates and AEs and SAEs from all sites. Safety concerns could trigger additional monitoring or onsite training and mentorship visits to take place by expert panel. Repeated 'non adherence' or 'failure' to comply would result in withdrawal of the site/principal investigator from the trial.

Standardisation of UK patient selection practice for surgery and laparoscopic ventral mesh rectopexy technique

The CapaCiTY trial 3 required the recruitment of 80 patients to undergo lapVMR. At the time of starting the programme this seemed easily achievable, with several UK centres performing > 100 such operations per annum. It became abundantly clear, however, that many centres' view of selecting patients for surgery did not agree with expert opinion (even at that time) in terms of defining surgical target pathophysiology (defined by INVEST) or in excluding patients with relative contraindications to surgery.

The development of consensus in respect to this and other surgical approaches to patients with CC was timely because it coincided with the rapid evolution of a media storm against the placement of pelvic mesh and worldwide class actions against surgeons and manufacturers of mesh. Although detrimental to recruitment, the increased rigour invoked by the programme in patient selection probably protected some patients (and their surgeons) from further harm.

Selection of surgeons to participate in CapaCiTY trial 3 also required submission of two videos for quality assurance of surgical technique. This highlighted not only unnecessary variation in technique but also some practices that could promote harm from mesh (e.g. use of polyester sutures). Again, although this actually delayed the study, it was probably beneficial to patients.

In regard to subsequent national and international scrutiny of mesh, work performed as part of this programme has featured in national guidance by learned bodies,[134] patient-facing information on consent for surgery and several news reports.[145]

Design features

Basic design

We used a stepped-wedge randomised trial design to permit observer-masked data comparisons between patients awaiting intervention and those who had undergone surgery. Contrary to most stepped-wedge trials, individual patients rather than clusters were randomised. In brief, eligible participants were randomised to three groups, with different delays before surgery (see *Figure 6*). In all groups there was a period of 4 weeks post eligibility to arrange the logistics of surgery (T–4 weeks to T0) and ensure that patients had returned to their normal life routine after various assessments. LapVMR was performed at T0 in group 1, T12 in group 2 and T24 in group 3. Unavoidably, participants were aware when surgery was undertaken; however, this fortuitously met the assumptions of the stepped-wedge design (i.e. no effect of treatment is expected until surgery has been performed). Efficacy outcome data were collected at equally stepped time points (T0, T12, T24, T36 and T48).

This was, in effect, a modification of a standard parallel-group, waiting-list control design, but with several advantages. First, a stepped-wedge design is more efficient and thus improves recruitment feasibility (the major hurdle of nearly all surgical trials). Despite the multicentre approach of this study, the problems of recruitment were manifest. Simulation demonstrated that a parallel-group design required a much larger sample size than that proposed for the current study at the same power. Second, the trial design meant that there was only a one-in-three chance (rather than one-in-two chance for a parallel group) of waiting 6 months for surgery, which was more acceptable to patients (see *Work programme 5*, *Patient and public involvement*).

Sample size calculation

Sample size was calculated using the primary clinical outcome (PAC-QoL score), but with a 1.0-point change deemed clinically important and sufficient to justify the cost and invasive nature of lapVMR. Previous surgical trials had shown a 1-point decrease in PAC-QoL score from pre surgery to 48 weeks (approximately 1 year) post surgery.[131] Using a stepped-wedge design, we hypothesised that PAC-QoL score at any time point during follow-up would be approximately 1.0 points lower than in preoperative participants.

Sample size was calculated by simulation using the 'simsam' package in Stata. We assumed that PAC-QoL score followed a normal distribution over all time points with a SD of 1.5 points and with a correlation between repeated assessments equal to 0.5 points. Simulation showed that detection of a 1.0-point difference in 6-month PAC-QoL score, with 95% power (purposely chosen to reflect the magnitude and risk of intervention) at the 5% significance level, required 34 participants in each of the three groups. Allowing for a 10% loss to follow-up, a sample size of 38 was needed per group (i.e. a total sample size of 114 patients across the three groups). Should the correlation between repeated assessments be < 0.5 points, a sample size of 114 will still provide at least 90% power for the study. This was calculated using the same simulation procedure with correlations of 0.3 and 0.1 points.

Randomisation procedure
Randomisation to the three trial groups (1 : 1 : 1) was stratified by sex, and female participants further stratified by centre (for the reasons outlined for CapaCiTY trial 2; in fact, only females were recruited).

Blinding
Patients and clinicians were necessarily aware of allocation to different waiting times. Quantitative outcomes were collected by investigators unaware of the before or after status of the patient in respect of surgery, and analysis was performed blind to allocation status.

Concomitant medications
Methods as for CapaCiTY trial 1, with recorded ad libitum use.

Statistical methods

Primary outcome
Total PAC-QoL scores at the time points T0, T12, T24, T36, T48, T60 and T72 in the three groups were analysed using a mixed linear regression model, with random effects for participants and a fixed effect of time since randomisation (potentially considering a random effect for time as well to relax the assumption of same time trend for each participant) to estimate mean differences between PAC-QoL score before and after lapVMR. The comparison of primary interest was between PAC-QoL score at 24 weeks after surgery and PAC-QoL score at baseline. A correction was included in the model to account for the small sample size. Missing data were imputed through multiple imputation by chained equations.

Secondary outcomes
Total PAC-SYM scores were analysed using the approach described in the paragraph above. All other secondary clinical outcomes derived from the standardised outcome framework were analysed only at 24 and 48 weeks post operatively. We present mostly descriptive statistics, with simple regression models used to obtain CIs for the results. Results obtained using the CC-BRQ and BIPQ-CC have been omitted pending further analysis.

Because of the nature of the intervention (i.e. pelvic surgery), a further outcome was included in CapaCiTY trial 3 (not included in CapaCiTY trials 1 and 2). The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12) is a self-administered questionnaire that evaluates sexual function in heterosexual women with urinary incontinence and/or pelvic organ prolapse. It has 12 items; responses are graded on a 5-point Likert scale from ‘never’ to ‘always’. Scores are calculated by totalling the scores for each question, with 0 indicating never and 4 indicating always. Reverse scoring is used for items 1–4. It can be used with up to two missing responses. To handle missing values, the sum is calculated by multiplying the number of items by the mean of answered items. The PISQ-12 scores can be reported only as a total or on a per-item basis.

All participants randomised to the three groups were analysed according to their allocation $\pm$ 2 weeks from the scheduled intervention date.

Cost-effectiveness
Patients were randomised in a stepped-wedge design to (1) immediate lapVMR, (2) lapVMR after a 12-week delay or (3) lapVMR after a 24-week delay. The design was chosen because of efficiency considerations and the logistical constraint of participants wanting surgery. The stepped-wedge design we adopted has three steps and features a closed cohort in which all patients spend time as controls and treated patients. Although the within-patient design is efficient, the step ‘placing’ creates particular challenges for the cost-effectiveness analysis. Economic analysis requires balanced time receiving alternatives to estimate incremental costs and QALYs. The value of surgery may be demonstrated over time frames of 1 or 2 years, and require a balanced pre-surgery period. Patient follow-ups were between 48 and 72 weeks post surgery. However, even using the screening visit as an approximate

–12-week time point, each patient had between only 12 and 36 weeks' pre-surgery follow-up. As has been reported, this trial was also severely hampered by under-recruitment. In an exploratory analysis, the trial was analysed as a simple pre–post within-patient design. Data were too sparse to use multiple imputation to cover an adequate pre-surgery period or postsurgery period beyond 48 weeks. Consequently, growth curve analyses (hierarchical generalised linear model) were used to describe and model pre-surgery and postsurgery trends. These models suggest that pre-surgery EQ-5D-5L scores and costs were constant and could reasonably be used to estimate EQ-5D-5L scores and costs at 48 weeks pre surgery using a 'first observation carried back' (FOCB) approach. The pre-surgery period was then conflated into a single period in subsequent analyses to reduce spurious precision. Postsurgery growth curve analysis found stable (non-surgery) costs and that EQ-5D-5L scores, although initially improving, returned to pre-surgery levels by 48 weeks, obviating the need for further extrapolation post surgery. An assumption of the approach taken is that there is no confounding with time (secular change). Although delay to surgery was to be explored in regression of costs and QALYs, the available sample is too underpowered to detect differences. No discounting was applied to economic data in CapaCiTY trial 3, reflecting the within-patient comparison of 48 weeks pre surgery and 48 weeks post surgery.

Recruitment

First recruitment occurred on 1 March 2016 and first intervention on 15 June 2016. Recruitment ended on 31 January 2019. A total of 28 (target 114) patients were randomised out of 81 screened (30.9%) from six sites. Reasons for screen failure are shown in *Figure 16*. Two sites opened but failed to recruit and one site failed to randomise; the remaining sites ($n = 6$) randomised 1–11 patients. Among the 28 patients randomised, nine patients were randomised to immediate surgery, 10 patients were randomised to a 12-week waiting list and nine patients were randomised to a 24-week waiting list. Six patients failed to complete the primary outcome at 24 weeks, among whom two dropped out of the study, which was therefore completed by 19 patients. The CONSORT flow diagram is shown in *Figure 7*.

Baseline characteristics

Table 26 shows the numbers and percentages of patients with baseline characteristics by trial group. Continuous variables (e.g. age) were summarised by treatment group using mean and SD (median and IQR if non-normally distributed). *Table 27* shows the data for outcome measures at baseline. These were comparable between the two groups for all major characteristics.

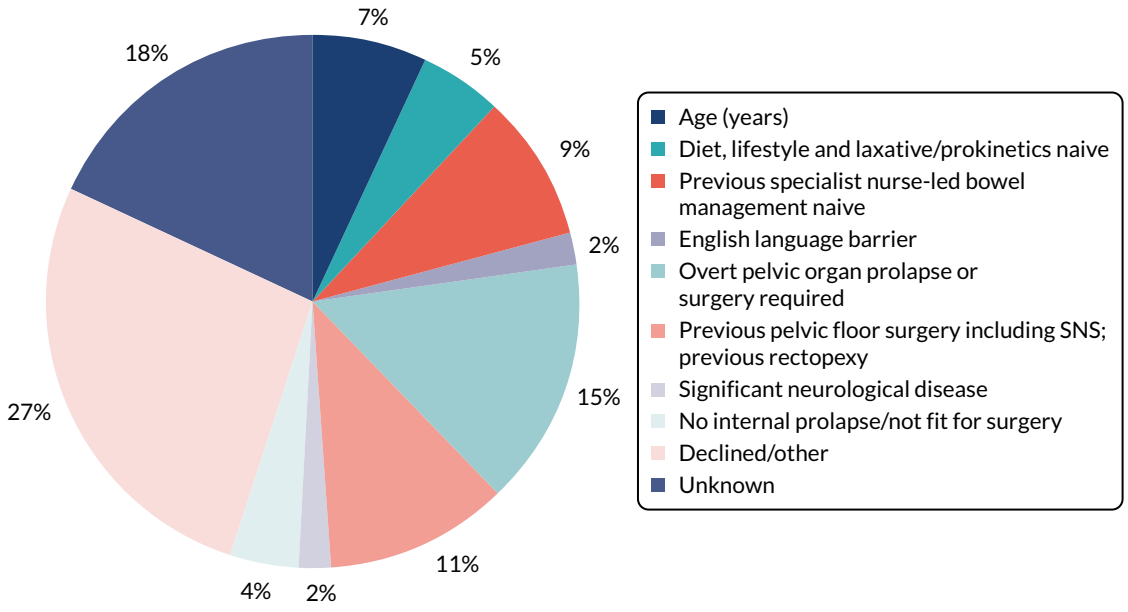

FIGURE 16 The CapaCiTY trial 3 screen failures. SNS, sacral nerve stimulation.

TABLE 26 The CapaCiTY trial 3 baseline data

Characteristic	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)[a]	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Referral method*, n *(%)				
Secondary care	5 (55.6)	6 (60.0)	4 (44.4)	15 (53.6)
Tertiary care	3 (33.3)	4 (40.0)	5 (55.6)	12 (42.9)
Other	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.6)
Demographic characteristic				
Sex, *n* (%)				
Female	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, *n* (%)				
Asian	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.6)
Black	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Mixed	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.6)
White	8 (88.9)	9 (90.0)	8 (88.9)	25 (89.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age (years)				
Mean (SD)	52.7 (14.3)	52.9 (14.4)	53.4 (9.8)	53.0 (12.6)
Median (IQR)	59.0 (39.0–66.0)	56.0 (42.0–64.0)	55.0 (49.0–58.0)	55.0 (42.0–64.5)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Past medical history*, n *(%)				
Total	7 (77.8)	9 (90.0)	6 (66.7)	22 (78.6)
Cardiovascular condition	4 (44.4)	3 (30.0)	1 (11.1)	8 (28.6)
Heart disease	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Hypertension	3 (33.3)	2 (20.0)	1 (11.1)	6 (21.4)
Hypercholesterolaemia	2 (22.2)	1 (10.0)	1 (11.1)	4 (14.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory condition	0 (0.0)	2 (20.0)	1 (11.1)	3 (10.7)
Asthma	0 (0.0)	2 (20.0)	1 (11.1)	3 (10.7)
COPD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal condition	5 (55.6)	3 (30.0)	2 (22.2)	10 (35.7)
IBS	3 (33.3)	3 (30.0)	1 (11.1)	7 (25.0)
Crohn's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ulcerative colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colonic polyps	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.6)
Other	2 (22.2)	0 (0.0)	1 (11.1)	3 (10.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TABLE 26 The CapaCiTY trial 3 baseline data (*continued*)

Characteristic	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)[a]	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Metabolic condition	0 (0.0)	3 (30.0)	4 (44.4)	7 (25.0)
Diabetes	0 (0.0)	1 (10.0)	1 (11.1)	2 (7.1)
Hypothyroidism	0 (0.0)	2 (20.0)	3 (33.3)	5 (17.9)
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haematological condition	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic condition	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genito-urinary condition	2 (22.2)	0 (0.0)	2 (22.2)	4 (14.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological/CNS condition	2 (22.2)	4 (40.0)	3 (33.3)	9 (32.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric condition	2 (22.2)	5 (50.0)	4 (44.4)	11 (39.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatological condition	1 (11.1)	3 (30.0)	1 (11.1)	5 (17.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal condition	3 (33.3)	2 (20.0)	3 (33.3)	8 (28.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other condition	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Past surgical history*, n *(%)				
Total	5 (55.6)	10 (100.0)	7 (77.8)	22 (78.6)
Abdominal operation	2 (22.2)	3 (30.0)	2 (22.2)	7 (25.0)
Gynaecological procedure	4 (44.4)	9 (90.0)	5 (55.6)	18 (64.3)
Proctological or perineal procedure	0 (0.0)	4 (40.0)	1 (11.1)	5 (17.9)
Neuromodulation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration (months) of constipation symptoms				
Mean (SD)	68.7 (36.9)	63.3 (31.6)	76.6 (55.4)	69.5 (41.3)
Missing, *n* (%)	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Previous lifestyle modifications*, n *(%)				
Total	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
Diet	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
Fluid	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)

continued

TABLE 26 The CapaCiTY trial 3 baseline data (*continued*)

Characteristic	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)[a]	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Exercise	7 (77.8)	10 (100.0)	7 (77.8)	24 (85.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alternative therapies*, n *(%)				
Total	1 (11.1)	1 (10.0)	1 (11.1)	3 (10.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Laxatives*, n *(%)				
Total	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antidiarrhoeals, *n* (%)				
Total	0 (0.0)	2 (20.0)	1 (11.1)	3 (10.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prokinetics, *n* (%)				
Total	1 (11.1)	3 (30.0)	2 (22.2)	6 (21.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nurse-led bowel management, *n* (%)				
Total	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Family history of bowel disease*, n *(%)				
IBS	2 (22.2)	2 (20.0)	2 (22.2)	6 (21.4)
IBD	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.6)
Gastrointestinal cancer	1 (11.1)	3 (30.0)	2 (22.2)	6 (21.4)
Other	1 (11.1)	2 (20.0)	0 (0.0)	3 (10.7)
Missing	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Sexual history (female participants only)*, n *(%)				
Sexually active	5 (55.6)	6 (60.0)	3 (33.3)	14 (50.0)
Child-bearing potential	4 (44.4)	4 (40.0)	4 (44.4)	12 (42.9)
> 1 year post menopausal	3 (33.3)	6 (60.0)	4 (44.4)	13 (46.4)
Surgically sterile	3 (33.3)	5 (50.0)	4 (44.4)	12 (42.9)
Contraceptive use (female participants only)*, n *(%)				
Total	2 (22.2)	2 (20.0)	3 (33.3)	7 (25.0)
Barrier	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Non-barrier	2 (22.2)	1 (10.0)	3 (33.3)	6 (21.4)
Missing	4 (44.4)	3 (30.0)	1 (11.1)	8 (28.6)
Past obstetric history (female participants only)				
Total, *n* (%)	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
Number of vaginal deliveries, mean (SD)	2.1 (1.1)	2.5 (1.1)	2.7 (1.0)	2.4 (1.0)
Number of caesareans, mean (SD)	1.0 (1.1)	0.1 (0.3)	0.4 (1.0)	0.5 (0.9)

TABLE 26 The CapaCiTY trial 3 baseline data (*continued*)

Characteristic	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)[a]	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Number of forceps/ventouse deliveries, mean (SD)	0.2 (0.7)	0.5 (0.7)	0.3 (0.7)	0.4 (0.7)
Number of episiotomies, mean (SD)	1.1 (1.1)	0.2 (0.4)	1.0 (1.2)	0.8 (1.0)
Number of obstetric tears, mean (SD)	0.6 (0.7)	0.4 (0.5)	0.6 (0.5)	0.5 (0.6)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Faecal incontinence symptoms*, n *(%)				
Total	7 (77.8)	9 (90.0)	7 (77.8)	23 (82.1)
Faecal urgency	4 (44.4)	8 (80.0)	5 (55.6)	17 (60.7)
Urge faecal incontinence	5 (55.6)	6 (60.0)	3 (33.3)	14 (50.0)
Passive faecal incontinence	4 (44.4)	6 (60.0)	3 (33.3)	13 (46.4)
Postdefaecation leakage	5 (55.6)	4 (40.0)	4 (44.4)	13 (46.4)
Difficulty wiping clean	6 (66.7)	5 (50.0)	4 (44.4)	15 (53.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pelvic organ prolapse symptoms*, n *(%)				
Total	6 (66.7)	5 (50.0)	7 (77.8)	18 (64.3)
Vaginal bulging	6 (66.7)	5 (50.0)	7 (77.8)	18 (64.3)
External rectal prolapse	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.6)
External uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.
a One patient dropped out before surgery (see *Figure 7*).

TABLE 27 The CapaCiTY trial 3 outcome measure data at baseline

Outcome measure	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
PAC-QoL score (points)				
Overall, mean (SD)	2.7 (0.6)	2.7 (0.6)	2.5 (0.8)	2.6 (0.6)
Missing, *n* (%)	1 (11.1)	0 (0.0)	1 (11.1)	2 (7.1)
Dissatisfaction, mean (SD)	3.1 (0.6)	3.1 (0.4)	3.2 (0.9)	3.1 (0.6)
Missing, *n* (%)	1 (11.1)	0 (0.0)	1 (11.1)	2 (7.1)
Physical discomfort, mean (SD)	2.7 (0.6)	2.9 (0.6)	2.7 (0.5)	2.8 (0.6)
Missing, *n* (%)	1 (11.1)	0 (0.0)	1 (11.1)	2 (7.1)
Psychosocial discomfort, mean (SD)	2.3 (0.9)	2.3 (0.9)	2.1 (0.9)	2.2 (0.9)
Missing, *n* (%)	1 (11.1)	0 (0.0)	1 (11.1)	2 (7.1)

continued

TABLE 27 The CapaCiTY trial 3 outcome measure data at baseline (*continued*)

Outcome measure	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Worries and concerns, mean (SD)	2.7 (0.7)	2.8 (0.7)	2.5 (1.0)	2.7 (0.8)
Missing, *n* (%)	1 (11.1)	0 (0.0)	1 (11.1)	2 (7.1)
PAC-SYM score (points)				
Overall, mean (SD)	2.3 (0.4)	2.1 (0.6)	2.3 (0.7)	2.2 (0.6)
Missing, *n* (%)	1 (11.1)	1 (10.0)	0 (0.0)	2 (7.1)
Stool symptoms, mean (SD)	2.7 (0.7)	2.1 (0.9)	2.5 (1.3)	2.4 (1.0)
Missing, *n* (%)	1 (11.1)	1 (10.0)	0 (0.0)	2 (7.1)
Abdominal symptoms, mean (SD)	2.3 (0.6)	2.5 (0.8)	2.4 (0.8)	2.4 (0.7)
Missing, *n* (%)	1 (11.1)	1 (10.0)	0 (0.0)	2 (7.1)
Rectal symptoms, mean (SD)	1.5 (0.7)	1.6 (1.2)	2.0 (1.2)	1.7 (1.0)
Missing, *n* (%)	1 (11.1)	1 (10.0)	0 (0.0)	2 (7.1)
Bowel frequency, number reported over 14 days (diary data)				
Attempts to empty bowels, mean (SD)	41.3 (16.2)	43.9 (27.6)	45.1 (23.2)	43.5 (22.0)
Missing, *n* (%)	2 (22.2)	2 (20.0)	2 (22.2)	6 (21.4)
Times stool was actually passed, mean (SD)	21.3 (14.5)	36.5 (18.7)	24.4 (20.8)	27.8 (18.6)
Missing, *n* (%)	2 (22.2)	2 (20.0)	2 (22.2)	6 (21.4)
Nature of bowel movement, number of days out of 14 (diary data)				
Laxatives used, mean (SD)	20.4 (5.7)	24.1 (6.6)	22.3 (6.6)	22.3 (6.2)
Missing, *n* (%)	2 (22.2)	3 (30.0)	2 (22.2)	7 (25.0)
Glycerine suppositories used, mean (SD)	27.7 (0.8)	27.7 (0.8)	27.6 (0.8)	27.7 (0.7)
Missing, *n* (%)	2 (22.2)	3 (30.0)	2 (22.2)	7 (25.0)
EQ-5D-5L: 'no problem' indicated,* n *(%)				
Mobility	4 (44.4)	2 (20.0)	4 (44.4)	10 (35.7)
Missing	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)
Self-care	1 (11.1)	1 (10.0)	1 (11.1)	3 (10.7)
Missing	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)
Usual activities	5 (55.6)	7 (70.0)	6 (66.7)	18 (64.3)
Missing	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)
Pain/discomfort	7 (77.8)	9 (90.0)	9 (100.0)	25 (89.3)
Missing	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)
Anxiety/depression	6 (66.7)	4 (40.0)	6 (66.7)	16 (57.1)
Missing	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)

TABLE 27 The CapaCiTY trial 3 outcome measure data at baseline (*continued*)

Outcome measure	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
EQ-VAS score (points)				
Total, mean (SD)	59.3 (14.3)	53.4 (23.0)	63.3 (17.3)	58.6 (18.6)
Missing, *n* (%)	2 (22.2)	1 (10.0)	0 (0.0)	3 (10.7)
PHQ-9 depression severity,* n *(%)				
None	5 (55.6)	2 (20.0)	3 (33.3)	10 (35.7)
Mild	1 (11.1)	4 (40.0)	3 (33.3)	8 (28.6)
Moderate	2 (22.2)	1 (10.0)	1 (11.1)	4 (14.3)
Moderately severe	0 (0.0)	0 (0.0)	2 (22.2)	2 (7.1)
Severe	0 (0.0)	2 (20.0)	0 (0.0)	2 (7.1)
Missing	1 (11.1)	1 (10.0)	0 (0.0)	2 (7.1)
GAD-7 anxiety severity,* n *(%)				
None	4 (44.4)	4 (40.0)	4 (44.4)	12 (42.9)
Mild	3 (33.3)	1 (10.0)	3 (33.3)	7 (25.0)
Moderate	0 (0.0)	2 (20.0)	1 (11.1)	3 (10.7)
Severe	1 (11.1)	2 (20.0)	1 (11.1)	4 (14.3)
Missing	1 (11.1)	1 (10.0)	0 (0.0)	2 (7.1)
St Mark's Incontinence Score (points)				
Total, mean (SD)	12.4 (3.6)	11.7 (5.9)	11.3 (4.7)	11.8 (4.7)
Missing, *n* (%)	1 (11.1)	0 (0.0)	1 (11.1)	2 (7.1)
PISQ-12 score (points)				
Total, mean (SD)	19.3 (7.1)	21.4 (6.7)	20.8 (5.4)	20.5 (6.1)
Missing, *n* (%)	2 (22.2)	3 (30.0)	0 (0.0)	5 (17.9)

Note that, owing to the lack of male participants, male sexual health outcomes are not summarised in this report.

Results: clinical effectiveness

Results for the primary outcome (i.e. PAC-QoL score) at 24 weeks (the primary end point) and at other time points are shown in *Table 28*. There was a substantive reduction in estimated PAC-QoL score at 24 weeks compared with the baseline of 1.09 points ($p = 0.0019$), exceeding that sought by design (1.0 points). A similar magnitude of change was observed for the modelled secondary outcome (i.e. PAC-SYM score). Reductions in scores were sustained at later time points, accepting a strong chance of attrition bias.

Secondary outcomes are shown in *Tables 29* (continuous) and *30* (binary). These show positive directional effects for nearly all outcomes, with some quite substantial improvements in measures, including > 25% scalar improvements in psychological measures (PHQ-9 score, GAD-7 score, St Mark's Incontinence Score and EQ-VAS score). Global patient satisfaction was 2.7 points at 24 weeks (i.e. closest to 'very satisfied'), although this dropped to 2.2 points (i.e. closest to 'moderately satisfied') at 48 weeks. This result was mirrored in the global patient improvement score (EQ-VAS score 0–100 points between 'no effect' and 'complete cure'), which was 72.2 points at 24 weeks and 56.5 points at 48 weeks.

TABLE 28 The PAC-QoL and PAC-SYM scores at baseline and follow-up points post surgery, with 95% CI and *p*-value for change from baseline to each follow-up point.

Time point	Number completing outcome evaluations	Observed mean score (points)	Estimated change from baseline score (points)	95% CI for change in score (points)	*p*-value for change in score (points)
PAC-QoL					
Baseline	26	2.63	–	–	–
12 weeks	23	1.35	−1.04	−1.54 to −0.55	0.0001
24 weeks	19	1.26	−1.09	−1.76 to −0.41	0.0019
36 weeks	19	1.47	−0.98	−1.87 to −0.10	0.0296
48 weeks	17	1.43	−1.07	−2.16 to 0.02	0.0552
60 weeks	9	1.22	−1.26	−2.56 to 0.05	0.0587
72 weeks	5	1.11	−1.38	−2.94 to 0.19	0.0840
PAC-SYM					
Baseline	26	2.24	–	–	–
12 weeks	23	1.15	−0.97	−1.41 to −0.53	0.0000
24 weeks	18	1.19	−0.92	−1.52 to −0.32	0.0029
36 weeks	19	1.25	−1.03	−1.80 to −0.26	0.0094
48 weeks	17	1.36	−0.97	−1.92 to −0.02	0.0444
60 weeks	9	1.19	−1.16	−2.28 to −0.03	0.0448
72 weeks	5	0.82	−1.51	−2.87 to −0.16	0.0289

All estimates are adjusted for time.

TABLE 29 Continuous secondary outcomes, with unadjusted estimate of difference in mean scores at 24 and 48 weeks post surgery compared with baseline

Time	*n*	Mean (SD)	Median (IQR)	Difference in means (95% CI)
PAC-QoL score (points)				
Dissatisfaction				
Baseline	26	3.1 (0.6)	3.1 (2.8–3.6)	Reference
24 weeks	19	1.8 (1.0)	1.8 (1.0–2.4)	−1.3 (−1.8 to −0.8)
48 weeks	17	2.1 (1.0)	2.0 (1.4–2.8)	−1.0 (−1.5 to −0.5)
Physical discomfort				
Baseline	26	2.8 (0.6)	2.8 (2.5–3.0)	Reference
24 weeks	19	1.3 (0.9)	1.3 (0.5–1.8)	−1.5 (−2.0 to −1.0)
48 weeks	17	1.6 (1.1)	1.5 (0.8–2.0)	−1.1 (−1.6 to −0.6)
Psychosocial discomfort				
Baseline	26	2.2 (0.9)	2.2 (1.5–3.0)	Reference
24 weeks	19	0.9 (0.7)	0.9 (0.3–1.5)	−1.3 (−1.8 to −0.8)
48 weeks	17	1.0 (0.9)	0.6 (0.1–1.4)	−1.2 (−1.8 to −0.7)

TABLE 29 Continuous secondary outcomes, with unadjusted estimate of difference in mean scores at 24 and 48 weeks post surgery compared with baseline (*continued*)

Time	*n*	Mean (SD)	Median (IQR)	Difference in means (95% CI)
Worries and concerns				
Baseline	26	2.7 (0.8)	2.9 (2.1–3.3)	Reference
24 weeks	19	1.3 (1.0)	1.2 (0.5–2.0)	−1.4 (−2.0 to −0.8)
48 weeks	17	1.4 (1.2)	1.0 (0.5–1.7)	−1.3 (−1.9 to −0.7)
Stool symptoms				
Baseline	26	2.4 (1.0)	2.6 (2.0–3.2)	Reference
24 weeks	18	1.2 (0.7)	1.3 (0.8–1.6)	−1.2 (−1.8 to −0.6)
48 weeks	17	1.6 (1.0)	1.4 (0.8–2.4)	−0.9 (−1.5 to −0.3)
Abdominal symptoms				
Baseline	26	2.4 (0.7)	2.4 (2.0–2.8)	Reference
24 weeks	18	1.4 (1.0)	1.3 (0.8–1.8)	−1.0 (−1.5 to −0.5)
48 weeks	17	1.5 (0.8)	1.5 (1.0–2.0)	−0.9 (−1.4 to −0.4)
Rectal symptoms				
Baseline	26	1.7 (1.0)	1.7 (1.0–2.0)	Reference
24 weeks	18	0.8 (0.5)	0.7 (0.3–1.0)	−0.9 (−1.4 to −0.3)
48 weeks	17	0.8 (1.0)	0.7 (0.3–1.0)	−0.9 (−1.4 to −0.3)
Diary data				
Bowel frequency: mean number of attempts to empty bowels over 2 weeks				
Baseline	22	43.5 (22.0)	45.5 (28.0–61.0)	Reference
24 weeks	20	22.9 (18.1)	19.0 (11.5–25.0)	−20.5 (−32.5 to −8.5)
48 weeks	15	30.6 (16.6)	30.0 (19.0–44.0)	−12.9 (−25.9 to 0.1)
Bowel frequency: mean number of times stool was passed over 2 weeks				
Baseline	22	27.8 (18.6)	19.5 (15.0–46.0)	Reference
24 weeks	21	17.3 (12.2)	14.0 (8.0–22.0)	−10.5 (−20.1 to −0.9)
48 weeks	15	21.3 (15.3)	19.0 (10.0–26.0)	−6.6 (−17.1 to 4.0)
Nature of bowel movement: mean number of days (out of 14) laxatives used				
Baseline	21	22.3 (6.2)	26.0 (15.0–28.0)	Reference
24 weeks	21	23.7 (4.7)	24.0 (21.0–28.0)	1.4 (−2.0 to 4.7)
48 weeks	15	22.7 (5.3)	25.0 (18.0–28.0)	0.4 (−3.3 to 4.1)
Nature of bowel movement: mean number of days (out of 14) glycerine suppositories used				
Baseline	21	27.7 (0.7)	28.0 (28.0–28.0)	Reference
24 weeks	21	26.5 (2.7)	28.0 (26.0–28.0)	−1.1 (−2.2 to −0.0)
48 weeks	15	27.4 (1.1)	28.0 (27.0–28.0)	−0.3 (−1.5 to 0.9)
EQ-VAS score (points)				
Baseline	25	58.6 (18.6)	60.0 (40.0–75.0)	Reference
24 weeks	20	73.7 (17.1)	77.0 (60.0–90.0)	15.1 (4.1 to 26.1)
48 weeks	17	68.2 (19.3)	70.0 (60.0–80.0)	9.6 (−1.9 to 21.1)

continued

TABLE 29 Continuous secondary outcomes, with unadjusted estimate of difference in mean scores at 24 and 48 weeks post surgery compared with baseline (*continued*)

Time	*n*	Mean (SD)	Median (IQR)	Difference in means (95% CI)
PHQ-9 score (points)				
Baseline	26	8.0 (6.5)	5.0 (4.0–11.0)	Reference
24 weeks	18	6.1 (6.0)	4.5 (2.0–9.0)	−2.0 (−6.0 to 2.0)
48 weeks	17	6.7 (7.0)	3.0 (2.0–10.0)	−1.3 (−5.4 to 2.7)
GAD-7 score (points)				
Baseline	26	7.1 (6.4)	6.5 (2.0–10.0)	Reference
24 weeks	18	5.0 (6.1)	2.5 (0.0–7.0)	−2.1 (−5.9 to 1.6)
48 weeks	17	4.4 (5.7)	2.0 (1.0–6.0)	−2.8 (−6.6 to 1.1)
Global patient satisfaction score (points)				
Baseline	NA	NA	NA	NA
24 weeks	18	2.7 (0.8)	3.0 (2.0–3.0)	NA
48 weeks	17	2.2 (1.3)	3.0 (1.0–3.0)	NA
Global patient improvement score (points)				
Baseline	NA	NA	NA	NA
24 weeks	18	72.2 (25.0)	80.0 (67.0–88.0)	NA
48 weeks	17	56.5 (34.6)	75.0 (25.0–80.0)	NA
St Mark's Incontinence Score (points)				
Baseline	26	11.8 (4.7)	13.0 (8.0–16.0)	Reference
24 weeks	16	8.7 (4.5)	8.5 (4.5–13.0)	−3.1 (−6.3 to 0.1)
48 weeks	17	8.7 (5.8)	8.0 (3.0–15.0)	−3.1 (−6.2 to 0.1)
PISQ-12 score (points)				
Baseline	23	20.5 (6.1)	21.0 (15.0–25.0)	Reference
24 weeks	12	18.8 (5.9)	18.0 (15.5–22.5)	−1.7 (−5.7 to 2.4)
48 weeks	12	17.3 (4.5)	17.0 (14.5–19.0)	−3.2 (−7.3 to 0.9)

NA, not applicable.
Male sexual health outcomes in the Male Sexual Health Questionnaire Ejaculatory Dysfunction Short Form (MSHQ-EjD Short Form) omitted owing to lack of male participants.

TABLE 30 Binary secondary outcomes, with unadjusted estimate of ORs, comparing scores at 24 and 48 weeks post surgery and baseline

Time point	*n/N* (%)	OR (95% CI)
PAC-QoL score, ≥ 1-point reduction		
Baseline	NA/NA	NA
24 weeks	11/18 (61.1)	NA
48 weeks	7/16 (43.8)	NA
EQ-5D-5L, problems indicated *Mobility*		
Baseline	10/25 (40.0)	NA
24 weeks	7/20 (35.0)	0.81 (0.24 to 2.73)
48 weeks	5/17 (35.0)	0.63 (0.17 to 2.33)

TABLE 30 Binary secondary outcomes, with unadjusted estimate of ORs, comparing scores at 24 and 48 weeks post surgery and baseline (*continued*)

Time point	*n/N* (%)	OR (95% CI)
Self-care		
Baseline	3/25 (12.0)	NA
24 weeks	4/20 (20.0)	1.83 (0.36 to 9.35)
48 weeks	2/17 (11.8)	0.98 (0.15 to 6.58)
Usual activities		
Baseline	18/25 (72.0)	NA
24 weeks	10/20 (50.0)	0.39 (0.11 to 1.34)
48 weeks	8/17 (47.1)	0.35 (0.09 to 1.26)
Pain/discomfort		
Baseline	25/25 (100.0)	NA
24 weeks	18/20 (90.0)	1.00[a]
48 weeks	17/17 (100.0)	1.00[a]
Anxiety/depression		
Baseline	16/25 (64.0)	NA
24 weeks	11/20 (55.0)	0.69 (0.21 to 2.29)
48 weeks	9/17 (52.9)	0.63 (0.18 to 2.22)

NA, not applicable; OR, odds ratio.
a High percentages made model fitting impossible.

Adherence to treatment

The numbers of patients (1) undergoing surgery as planned and (2) reporting that they were taking confounding medications, including those bought over the counter and numbers of confounding medications used, are presented by trial group in *Table 31*. As shown, concomitant medication use was high (i.e. by almost all patients).

Safety analyses

Laparoscopic ventral mesh rectopexy has a number of specific complications in addition to the general risks of surgery. Data on these complications are in the public domain and can be considered to be expected events. However, these were still recorded for outcome reporting. The study (not being of a medicinal product) did not record unrelated AEs, and related AEs and SAEs were small in number, with only two related SAEs reported (*Table 32*).

TABLE 31 The numbers of patients receiving surgery as planned and use of concomitant medication

Characteristic	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Number of patients who underwent surgery	9	9	9	27
Number of patients reporting the use of concomitant medications	9	8	7	24
Number of concomitant medications reported	64	80	56	200

TABLE 32 The CapaCiTY trial 3 AEs

Variable	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Related AEs				
Number of patients reporting AE	8	7	1	16
Number of AEs reported by category				
Abdominal pain	2	2	0	4
Anal/rectal pain or discomfort	1	3	0	4
Bloating	0	1	0	1
Constipation	1	0	0	1
Haemorrhoids	1	0	0	1
Loose motions	0	1	0	1
Rectal bleeding	1	1	0	2
Vaginal/perineal bulge	2	1	0	3
Miscellaneous	4	8	0	12
Severity				
Mild	5	5	0	10
Moderate	7	12	1	20
Causality				
Unlikely to be related	3	4	1	8
Possibly related	4	7	0	11
Definitely related	3	6	0	9
Action				
No action taken	8	7	1	16
Withdrawal	1	0	0	1
Concomitant medication	2	9	0	11
Non-drug therapy	1	0	0	1
Hospitalisation	0	1	0	1
SAEs[a]				
Number of patients reporting SAEs	2	3	0	5
Number of SAEs reported that require hospitalisation or prolongation of existing hospitalisation				
Unlikely to be related	1	0	0	1
Possibly related	0	2	0	2
Definitely related	1	1	0	2
Expectedness				
Expected	1	2	0	3
Unexpected	1	1	0	2

TABLE 32 The CapaCiTY trial 3 AEs (*continued*)

Variable	Group 1: lapVMR performed at T0 (*N* = 9)	Group 2: lapVMR performed at T12 (*N* = 10)	Group 3: lapVMR performed at T24 (*N* = 9)	Total (*N* = 28)
Action taken				
No action	0	1	0	1
Concomitant medication	1	1	0	2
Non-drug therapy	1	0	0	1
Hospitalisation	0	1	0	1

a None of the SAEs was identified as related to a treatment; no unresolved SAEs were reported.

Results: cost-effectiveness

Summary and completeness of data

Patients were allocated randomly to lapVMR with either immediate surgery or surgery after a 12-week or 24-week delay. The trial under-recruited (25 out of a planned 114 patients), making analysis exploratory. Variables used to estimate costs and QALYs are described in *Table 33*. For brevity, prescription and community health-care resources are shown costed and aggregated by period before and after surgery. Non-interventional costs were small and stable in the periods before and after surgery, compared with the cost of surgery itself (£4941 per patient). All patients had a minimum follow-up period from 12 weeks pre surgery to 48 weeks post surgery. Pre-surgery and postsurgery follow-up could be extended by up to 24 weeks depending on the delay in allocation to surgery. Completeness of cost and QALY data was reasonable over the period of common follow-up (−12 to 48 weeks) but diminished outside this follow-up window, reflecting a combination of allocation and missed visits.

TABLE 33 The CapaCiTY trial 3 economic analysis variables (£, 2018)

Cost (£, 2018)				QoL, EQ-5D-5L score (points)			
Period[a]	Mean (SD)	SD	*n*	Period[a]	Mean (SD)	SD	*n*
−48 to −36 weeks[b]	–	–	0	−48 weeks[b]	–	–	0
−36 to −24 weeks[c]	39	66	7	−36 weeks[c]	0.664	0.145	9
−24 to −12 weeks[c]	138	259	15	−24 weeks[c]	0.596	0.224	17
−12 to 0 weeks	82	147	23	−12 weeks	0.637	0.198	22
0 to 12 weeks	85	126	22	0 weeks	0.613	0.286	23
12 to 24 weeks	126	264	21	12 weeks	0.731	0.150	24
24 to 36 weeks	64	80	17	24 weeks	0.671	0.235	20
36 to 48 weeks	146	194	16	36 weeks	0.701	0.196	19
48 to 60 weeks	120	95	7	48 weeks	0.618	0.279	17
60 to 72 weeks	126	127	6	60 weeks	0.719	0.225	10
–	–			72 weeks	0.809	0.118	5
FOCB							
−48 to −36 weeks	71	191	27	−48 weeks	0.637	0.172	26
−36 to −24 weeks	71	191	27	−36 weeks	0.637	0.172	26
−24 to −12 weeks	90	210	27	−24 weeks	0.629	0.192	25

continued

TABLE 33 The CapaCiTY trial 3 economic analysis variables (£, 2018) (*continued*)

Cost (£, 2018)				QoL, EQ-5D-5L score (points)			
Period[a]	Mean (SD)	SD	*n*	Period[a]	Mean (SD)	SD	*n*
LOCF							
36 to 48 weeks	141	189	17	48 weeks	0.627	0.257	20
48 to 60 weeks	130	137	17	60 weeks	0.627	0.283	20
60 to 72 weeks	121	124	18	72 weeks	0.635	0.278	21
Health-care cost							
−48 to 0 weeks[d]	239	442	23	−48 to 0 weeks[d]	0.571	0.164	19
0 to 48 weeks	468	452	15	0 to 48 weeks	0.639	0.184	12
Δ[e]	5252	564	14	Δ[e]	0.018	0.121	10
Societal cost[f]							
−48 to 0 weeks	1131	1762	23	–	–	–	–
0 to 48 weeks	2835	4474	15	–	–	–	–
Δ[g]	6540	4863	14	–	–	–	–

LOCF, last observation carried forward.
Subtotals may not sum to totals because of different numbers of patients contributing.
a Includes (non-surgery) prescription drugs, hospital and community health visits.
b No patients had data observed at this time point or for this period.
c Because of the allocated delay to surgery, patients had between 12- and 36-week pre-surgery data.
d Pre-surgery costs and QALYs estimated by FOCB.
e Incremental health-care cost = cost of surgery + cost (0 to 48 weeks) − cost (−48 to 0 weeks).
f Includes days lost from usual activity/work.
g Incremental societal cost.

To construct an informative exploratory analysis, a simple pre–post design was employed, with the three trial groups aligned and the time of surgery of each group becoming T0. Exploratory growth curve analysis of the postsurgery period found a stable cost consistent with a constant value over each period but an increasing and then decreasing EQ-5D-5L score over the 48-week period following surgery. Using last observation carried forward (LOCF) from 48 weeks to compensate for diminishing data, the EQ-5D-5L score was consistent with a constant value beyond 48 weeks. An incremental analysis would then require costs and QALYs estimated 48 weeks before to 48 weeks after surgery. Comparison of observed data and growth curve analysis using FOCB from −12 weeks found that costs and EQ-5D-5L scores were stable and consistent with a constant value over the pre-intervention period. Consequently, costs and EQ-5D-5L scores were estimated for the entire pre-surgery period (−48 to 0 weeks) using the FOCB approach because data were too sparse to attempt imputation. Multiple imputation was used in the base-case model to manage missing values in the pre-surgery period and the postsurgery periods from 0 to 48 weeks.

Cost-effectiveness analyses

The base-case model is reported in *Table 34*. Comparing pre-surgery and postsurgery periods, intervention led to a significant increase in cost (£5012, 95% CI £4446 to £5322), similar to the cost of surgery, and a modest and imprecise increase in QoL (0.043 QALYs, 95% CI −0.005 to 0.093 QALYs). The ICER of £115,512 per QALY is visualised using the ICER plane in *Figure 17*. NMB values were negative for surgery across the commonly used range of WTP thresholds, indicating a lack of cost-effectiveness. These findings are presented as a CEAC showing the probability of being cost-effective at various WTP thresholds. At the NICE-recommended WTP of £30,000 per QALY, the probability that surgery is cost-effective is 0%. The EVPI (per subject) reflects the opportunity loss of ongoing uncertainty and suggests that there is no requirement for further research.

TABLE 34 The CapaCiTY trial 3 cost-effectiveness analysis (£, 2018)

IapVMR vs. no IapVMR	ICER (95% CI)	IC (95% CI)	IQ (95% CI)	CEAC *p*-value[a]	CEAC *p*-value[b]	NMB[a] (95% CI)	NMB[b] (95% CI)	EVPI[b]
Base case	115,512 (53295 to [c])	5012 (4446 to 5322)	0.043 (−0.005 to 0.093)	0.000	0.000	−4346 (−5115 to −3517)	−3693 (−5098 to −2166)	0
Complete case	204,374 (49308 to [c])	5020 (4757 to 5288)	0.025 (−0.056 to 0.101)	0.000	0.000	−4668 (−5915 to −3436)	−4308 (−6760 to −1939)	0
Sensitivity analysis[d]	–	–	–	0.000	0.000	−4354 (−5351 to −3378)	−3681 (−5181 to −2087)	0

a Probability cost-effective at WTP threshold of £15,000 per QALY.
b Probability cost-effective at WTP threshold of £30,000 per QALY.
c Denotes a dominated strategy: increase in cost and decrease in QALYs.
d Univariate regression (NMB) of base case.

Note
Bootstrapped 95% CIs; median ICERs.

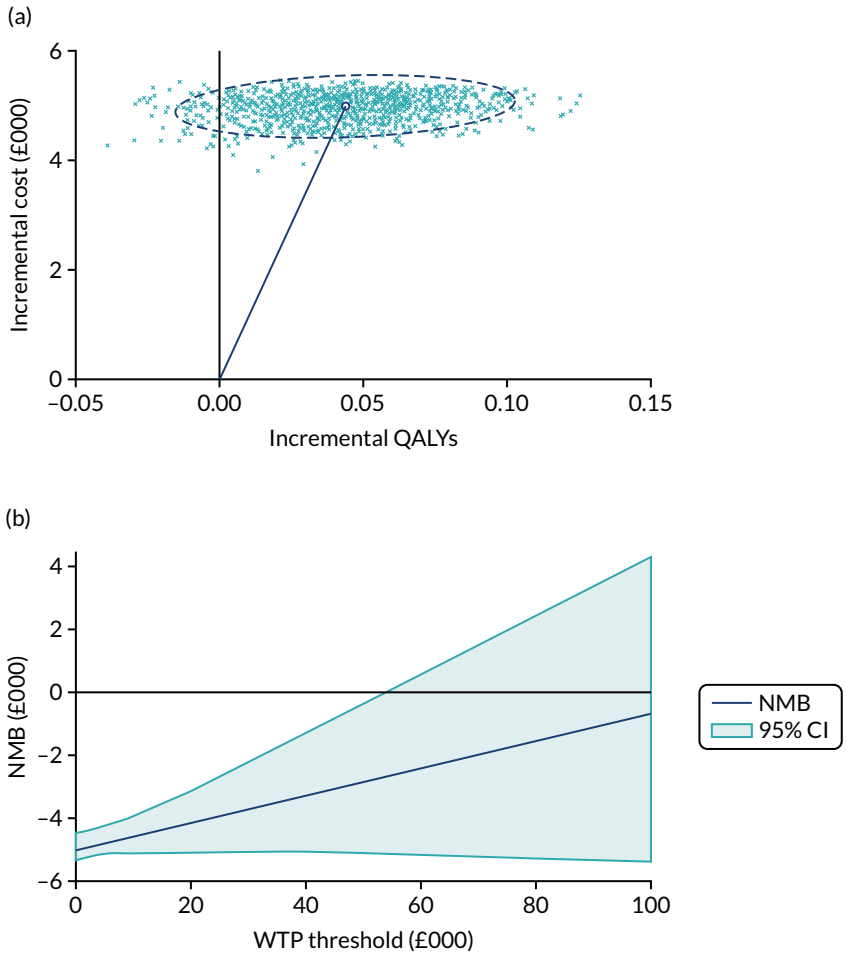

FIGURE 17 The CapaCiTY trial 3 cost-effectiveness analysis: base case. (a) ICER plane [the credible region (dashed circle) shows where 95% of estimates lie]; (b) incremental NMB; (c) CEAC; and (d) EVPI. (*continued*)

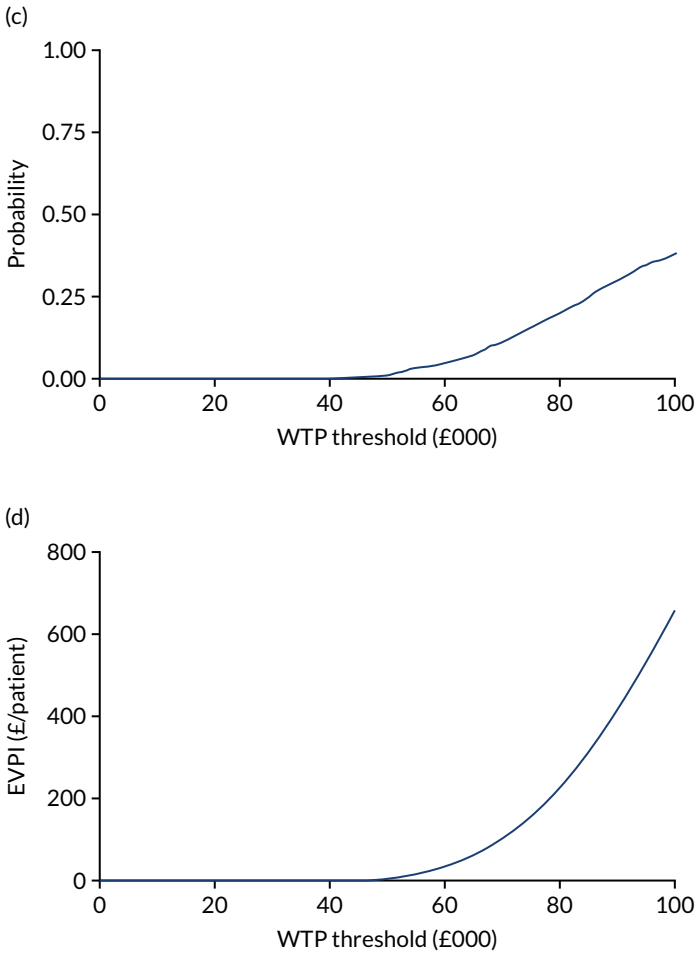

FIGURE 17 The CapaCiTY trial 3 cost-effectiveness analysis: base case. (a) ICER plane [the credible region (dashed circle) shows where 95% of estimates lie]; (b) incremental NMB; (c) CEAC; and (d) EVPI.

In *Figure 17a*, the ICER plane shows that lapVMR resulted in a significant increase in costs but modest and imprecise increase in QALYs. In *Figure 17b*, the incremental NMB shows that investing in lapVMR at commonly used WTP thresholds appears to deliver a loss to the health-care system compared with alternatives. In *Figure 17c*, the CEAC shows that there is a very low probability that lapVMR is cost-effective. In *Figure 17d*, the EVPI suggests that there is little value to the health-care system of further research in this field unless the WTP threshold was considerably higher than commonly used thresholds.

The complete-case analysis (using the FOCB estimate of pre-surgery cost) is also presented in *Table 34*. Although the numbers contributing are small, the findings are statistically similar to the base case, if less precise. Given the very small numbers in the trial, as a sensitivity analysis the base-case model was re-estimated as a univariate regression (NMB at various WTP thresholds). The findings were very similar: at a WTP of £30,000 per QALY, the probability that surgery was cost-effective was 0%.

Results: patient experience and qualitative analysis

Emergent themes are presented in this section. Numbers in square brackets refer to the numbered quotations in *Appendix 2*, *Quotations from participants contributing to qualitative analysis in all three trials, CapaCiTY trial 3: laparoscopic ventral mesh rectopexy*.

Making the decision for surgery

Nine out of the 10 interviewees opted for lapVMR surgery. For some, the decision to undergo surgery was a much-welcomed pragmatic option [1]. Others appeared to go through a longer deliberation process about potential adverse effects of the surgery, including the recently publicised issues around mesh usage in surgery [2]. The health-care professional's detailed explanation of the surgery, as well as

trust in the surgeon and wider bowel team, seemed to mitigate these concerns. For one patient, the reasons for not opting for surgery at this time included several current physical and mental health issues. This patient had chosen to manage her CC with a change in diet, TAI, suppositories and laxatives, as advised by health-care professionals.

Patient surgical experience

A few patients experienced surgical delays, cancellations and pathway difficulties due to administration or cross-departmental communication issues. A number reported a very good hospital stay experience and described how they felt supported by the surgical and wider health-care team. Some patients reported that the surgery was better than they had initially expected [3]. However, a few patients did report negative experiences during their hospital stay. These did not appear to be related to the surgery itself, but rather to the before and after care provided on the wards.

Patient postoperative experience

The level of postsurgical pain seemed to vary. For some, pain was not much of an issue [4], whereas for others postoperative pain was a significant feature [5]. Recovery times also varied, with a couple of patients going back to work within weeks. However, for several it took between 6 weeks and 9 months to fully recover postoperatively.

Surgical results

Some patients described how their bowel functioning was better immediately after surgery [6]. For others, it took a few weeks to start seeing improvement. However, for a few patients the surgery did not seem to improve their constipation [7]. Some patients have reported continued success and a better QoL both mentally and physically [8] and would recommend the surgery to someone who was experiencing similar bowel issues.

For others, the surgery has corrected some but not all issues, such as being able to pass stools in a timely manner. Thus, for some, it was not the 'miracle cure' they were hoping for [9]. A few patients reported that, although surgery initially seemed to be addressing their problematic bowel issues, they were now re-experiencing these problems [10].

Postoperative behavioural changes

Some patients changed their diet and fluid intake after surgery to better manage their bowels and to promote continued success, and others had a healthy diet prior to surgery and continued to maintain this. Some patients reported using laxatives from time to time after surgery, but that this use was much less frequent than before.

Patient concerns

A few patients, particularly those who were re-experiencing their previous symptoms, reported concerns about a prolapse recurring as well as new defaecation pain. For a few patients, there had been additional concerns about whether or not mesh use played a role in continued pain following surgery.

Mesh in the media

Although the study had the full backing from national expert groups such as the Pelvic Floor Society, negative coverage of mesh use in the media coincided with the start of the study [11]. This affected the wider elements of the study in terms of patient participation.

Staff experiences

Because of the media coverage there was reluctance from surgeons to recruit patients for the study and to surgery in general, or surgeons decided to no longer perform lapVMR at all. These media concerns have led to surgeons directly expressing anxieties [12]. In addition, some hospitals erred on overemphasising the risks involved, providing patients with multiple consent forms, which potentially exacerbated patient anxieties about lapVMR. Equally, entire organisations chose to no longer offer the surgery because of litigation concerns.

Documents outlining the differences between the gynaecological mesh issues (in the media) and the current lapVMR surgery helped to clarify some patient concerns, as did surgical mentoring and patient tracking databases. However, recruitment continued to be severely affected by the negative media coverage [13]. Developing one nationally recognised information sheet and lapVMR surgical certification may assist with patient and surgeon anxieties in future.

Some staff stated that CapaCiTY trial 3 did not appear to affect current clinical practice. However, others did acknowledge that the research affected practice and/or current practice affected the research procedure owing to protocol restrictions and scheduling issues.

Surgeons noted that lapVMR surgery is technically challenging, particularly if the patient has additional medical complications. Furthermore, owing to the technical nature of the operation, extensive experience of carrying out lapVMR surgeries is deemed necessary to perform the procedure, limiting the number of surgeons able to offer this operation. The research team attempted to mitigate any potential surgical variation by reviewing operation videos; however, disparity still existed.

Although the surgical video review embedded in the current study attempted to solve the issue of operational variation, it presented additional challenges around:

- patient consent deviations
- potential reluctance of sites/surgeons participating owing to feeling scrutinised
- professional feedback difficulties, which may have contributed towards administrative video review delays.

Anxieties around potential legal issues, lack of experienced lapVMR surgeons and surgeons possibly feeling scrutinised by video review could have contributed towards the difficulty of recruiting surgical staff to take part in CapaCiTY trial 3 interviews (in addition to the patient recruitment issues). However, the general sense from the interviewed staff was that lapVMR is helpful for the majority of patients, although staff also recognise that some patients (particularly those who have multiple medical issues) may not experience lasting beneficial results.

Appendix 2 Other outputs arising from the programme

CapaCiTY trial 1: intervention protocols

Habit training

Sessions (minimum 3, maximum 4; ≈ 60 minutes each).

This will use a standardised pro forma.

- Participants receive a written information leaflet covering normal bowel function, causes of constipation, diet and fluid advice, and getting into a good bowel habit.
- Participants receive a review of written information using locally available teaching tools such as models or diagrams.
- Participants receive advice to stop using all laxatives, including drugs that the *British National Formulary*[146] describes as having a laxative effect or over-the-counter herbal teas that contain strong purgatives. Glycerine suppositories (one or two) as rescue if there is no stool for 3 days is allowed. No use of irrigation devices or enemas.
- Participants encouraged to follow a daily routine: sit on the toilet 20–30 minutes after first meal and/or hot drinks (sooner if urge felt).
- Participants instructed that they can attempt defaecation after meals or when urge is felt, but no more than three times per day.
- Participants instructed that they should sit on the toilet with knees bent in a 45-degree position, with feet elevated on stool or equivalent, and abdominal brace and breathe while performing anal relaxation.
- Participants instructed that they must attempt to push for only 5–10 minutes maximum.
- Defaecation manoeuvres taught while the patient is positioned sitting on a chair, with verbal coaching to breathe while pushing.
- Participants strongly discouraged from multiple attempts and prolonged straining.
- Participants instructed that there must be no digitation anally.
- Where appropriate, participants taught rectocele (vaginal), perineal and perianal splinting.
- Therapists prohibited from using digital rectal exam to train manoeuvres.
- Participants receive diet and lifestyle advice (e.g. moderate but not excessive fibre; moderate but not excessive fluid intake; increase exercise, such as walking, if possible).
- Only participants with evacuation difficulty and/or perineal descent taught pelvic floor exercises.
- Participants receive optimistic encouragement and personal attention.
- Participants receive suggestions about what to work on until next meeting.
- Therapists to complete relevant sections in participant booklet.

Habit training and direct visual biofeedback

- Biofeedback balloon and catheter/probe connected to computer monitor. Patient lying in lateral position facing computer screen (supine if unable to lie in lateral position). Probe taped or held into position.
- Resting pressure noted (using event recorder). Squeeze pressure noted.
- Rectal balloon inflated with air (2 ml/second) to assess first sensation and urge volume. Volumes noted. Maximum = 360 ml.
- Rectoanal inhibitory reflex elicited with 50-ml aliquots and rapid inflation with air (30 ml/second); volume to first urge and the effect on resting pressure noted. Maximum = 150 ml.

- Coaching to evacuate with 60 ml of water (one syringe full) in the balloon. Participant attempts balloon expulsion and the effect on anal pressure noted.
- Attempts to relax while pushing to expel balloon are monitored. Participant instructed to push and breathe, with emphasis on needing to push from the waist while relaxing the anus. Propulsive effort noted. A minimum of three 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 ensured.
- HRAM can be used to coach pelvic floor exercises if indicated.
- 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.

Quotations from participants contributing to qualitative analysis in all three trials

Synonyms and group allocation are indicated after each quotation.

CapaCiTY trial 1: habit training with or without biofeedback with or without standardised radiophysiological investigations

1. *It was good; indeed, to know that quite early on, that there was nothing serious [after INVEST], that has helped.*

   Brian, HTBF with INVEST

2. *Well, relief in one way because they didn't sound like a lot of fun. But also, perhaps, a little regret because I thought I might get better treatment if I had. So a mixture.*

   Beth, HT

3. *My constipation is stress related and psychologically related and talking to somebody about it really helped.*

   Francesca, HT

4. *Meeting people that it was OK to be like this around, and being OK to talk about it, that they understood and not just thinking 'is this just me?', 'is this just me and am I going to live like this for the rest of my life?'*

   Helen, HT

5. *I'd got into a very bad routine and I learned more about improving . . . the dietary side of things . . . and that includes fluids, which I've always been very bad at having enough [of].*

   Anne-Marie, HT with INVEST

6. *I've introduced fibre . . . fibre is more the crucial thing.*

   Edward, HTBF

7. *One really good thing for me was becoming aware, after all these years, that I'd actually been working against nature, in that I was given advice to be breathing – which, to me, was very, very useful, because I had been doing the opposite, which basically means tightening . . . the rectum instead of relaxing it.*
Anne-Marie, HT with INVEST

8. *Having the nurse talk to me about how the bowels actually work, how the problems that my bowels actually have – I mean that's really helped me. It has reassured me and I don't really get as stressed out as I used to. I don't have any accidents [faecal incontinence] like I used to either.*
Teresa, HT with INVEST

9. *I find [the booklet] very informative, especially to the patient and also to the clinician as well, especially if they are not, you know, they are not so familiar yet with the normal evacuation process.*
Bill, clinical intervention nurse

10. *It's much easier for me when I use a [foot]stool. So what I even did – I bought myself a portable stool, and took it with me when we went on holidays.*
Lauren, HTBF with INVEST

11. *I guess it's the reiteration, because a lot of the stuff that he's telling me is stuff that I kind of know already, insoluble and soluble fibre stuff, prune juice, I've been doing that for ages now. Exercise. But again it's just the reiteration and kind of focusing on what I need to concentrate on.*
Samantha, HT

12. *I certainly feel that there's been some improvement.*
Linda, HT

13. *I did have some patients that really grasped using the screen and the images and that really helped them understand their condition and enabled them to be able to use the map in the right way and improve, so I found that really interesting to see.*
Becky, physiologist

14. *I personally felt that when the way that I treated the patients before CapaCiTY came along, worked exceptionally well and patients were improving. I don't think the machine added any benefit at all.*
Maria, clinical intervention nurse

15. *It was a little bit undignified . . . but I'm normally very OK about that sort of thing, I just get on with it.*
Kate, HTBF

16. *The fact that I'm off the [laxatives] is the best thing. I'm still having interventions and it's not perfect, but it's not like it used to be.*
Lauren, HTBF with INVEST

17. *I have no qualms about recommending it to absolutely anybody.*
Edward, HTBF

18. *It takes longer setting up and takes another 15–20 minutes.*

Shaunett, clinical intervention nurse

19. *I just didn't like using [the biofeedback machine] and that might be because I'm not great with change or adopting something new.*

Maria, clinical intervention nurse

CapaCiTY trial 2: transanal irrigation

1. *We're very enthusiastic because we've seen the results and we know that it works. So if we're really positive about it, I think that really helps. And bringing the patient along with you as well, so you've got to build a good rapport with the patient and bring them along with you.*

Bernadette, clinical intervention nurse

2. *I think the opportunity to practice during that visit with the nurse was extremely helpful, because there were some initial 'so I do it this way, do I do it that way?' things I could get immediate feedback on so that was very helpful.*

Warren, high-volume TAI, continuing use

3. *She offered me the chance to do it [in the clinic] but I just did it at home, it seemed quite straightforward . . . it's still something that I feel a bit embarrassed talking about, or doing, so I just preferred to do it at home.*

Derek, high-volume TAI, continuing use

4. *I was still worried about doing it, because you're doing it once with the nurses and then you're coming home and you're on your own. But as I say, I knew they were on the end of the phone, and I knew I could phone them.*

Rita, high-volume TAI, continuing use

5. *You're trying to take in a lot of information all at once with a procedure that feels really unnatural, so I think there's lots of kind of sequential things that could go wrong . . . not wrong, but just kind of, are not entirely clear. So even with all that really good explanation and opportunity [to practice in clinic] there was still a lot of confusion for a wee while.*

Warren, high-volume TAI, continuing use

6. *It does take a bit of time to get used to it, because it's a strange sensation, but once you do it's quite straightforward to do.*

Josephine, high-volume TAI, continuing use

7. *It was fine; easy to do.*

Lacey, low-volume TAI, continuing use

8. *In the first 3 or 4 days I got what felt like period pain, in my abdomen, just the pressure of the water being pumped up, but then after, nothing in my abdomen after that. It just feels strange. I wouldn't say that it's painful, it just feels strange using a catheter.*

   Laurella, high-volume TAI, continuing use

9. *[I was] quite happy to do the low[-volume] one . . . I thought the higher[-volume] one would be more like the colonic irrigation, more painful or more intense.*

   Lacey, low-volume TAI, continuing use

10. *You fit it into your daily routine easily, it's quick to use.*

    Elizabeth, high-volume TAI, discontinued use

11. *Sometimes it's quite restrictive, in that it's hard to fit it into my daily life. Sometimes I get into a routine with the children and sort of forget about doing it.*

    Lacey, low-volume TAI, continuing use

12. *I think for a couple of months, possibly a bit longer, maybe for a month after using it or a bit longer, it was still hit or miss, but more recently it has been absolutely fantastic and it does work every time.*

    Laurella, high-volume TAI, continuing use

13. *I am absolutely over the moon with it and I'm happy with how it's all ended [up]. Compared to how I am now to how I was I'm like a different person because I feel clean all the time.*

    Pamela, low-volume TAI, continuing use

14. *100% satisfied. I'll go on holidays now . . . I'm alive again, I feel like I'm bubbly inside . . . I can go outside, I can do a lot of walks.*

    Derek, high-volume TAI, continuing use

15. *I don't suffer from chronic constipation anymore. So I used to go maybe once a week and that's how my life was. I used to joke that every Wednesday was my poo day. So this has helped me so much, I can only thank the team for transforming my life.*

    Pamela, low-volume TAI, continuing use

16. *It's the leakage, you have to change once or twice until it stops and then after that it's fine, but there's always that bit of leakage coming out after and with me.*

    Rebecca, high-volume TAI, continuing use

17. *Sometimes this group of patients are able to get results straight away, particularly with the high-volume kit; however, some do need to persevere in order to see the results as it may take time to adapt the system to meet the person's particular needs.*

    Joyce, clinical intervention nurse

CapaCiTY trial 3: laparoscopic ventral mesh rectopexy

1. *I sort of jumped at the chance . . . I just thought if I could just empty naturally, then it would make life a lot easier.*

   Rachel, post surgery

2. *Obviously [I had] fears, lots of fears about having it done, whether it was the right thing to do . . . it was all the publicity about mesh.*

   Camilla, post surgery

3. *I think the actual surgery – afterwards, it was better because I thought I was going to be all scarred down below but it was all done in my tummy, which was better than what I expected . . . The actual recovery from the surgery, that went quite quickly.*

   Rita, post surgery

4. *There wasn't a lot of pain with it.*

   Peggy, post surgery

5. *I did have a lot of pain post op. I had quite a severe nerve pain on my right-hand side; that gave me more problems than the actual pain in my bottom area. That took about 3 or 4 months to calm down.*

   Esther, post surgery

6. *The treatment was excellent and, as I say, the bowel sensation down below literally disappeared immediately and I don't have to use gloves and a finger to get all the poo out.*

   Lilian, post surgery

7. *[The surgery] didn't change anything really.*

   Camilla, post surgery

8. *I used to get very down before the operation and then afterwards even my son noticed and said 'you seem cheerful mum', and I said 'yeah, I feel quite good actually'.*

   Amanda, post surgery

9. *It wasn't the miracle cure that I thought it might be, although [the surgeon] didn't promise me a miracle cure. But he said, you know, that it should improve my quality of life. I don't think it has really.*

   Rachel, post surgery

10. *My prolapse is back, the pain's back, it was about 10 months after the surgery that my prolapse came back and I'm waiting to see the surgeon again. I was told that it should last about 10 years, but it lasted 10 months.*

    Esther, post surgery

11. *There's been a massive coverage in the media about the negatives of using mesh and how it introduces long-term issues for the patient.*

Angela, research team member

12. *It's a dangerous place being a pelvic floor surgeon. But you've got to keep yourself buoyed up by the fact that the majority of patients do well. Otherwise you wouldn't do it at all. There is a danger that we all stop doing this because of the small minority of patients that are not happy.*

Christopher, surgeon

13. *We were just . . . getting [the study] off the ground when this all blew up and sabotaged it. And of course, the question is more relevant than ever now with the mesh problems. The study aimed to address [this], which is the sort of horrendous irony of it really.*

Marshall, surgeon

EME
HS&DR
HTA
PGfAR
PHR

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