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RANDOMISED CONTROLLED TRIAL

Habit training versus habit training with direct visual biofeedback in adults with chronic constipation: A randomized controlled trial

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Abstract

Aim: The aim was to determine whether specialist-led habit training using Habit Training with Biofeedback (HTBF) is more effective than specialist-led habit training alone (HT) for chronic constipation and whether outcomes of interventions are improved by stratification to HTBF or HT based on diagnosis (functional defaecation disorder vs. no functional defaecation disorder) by radio-physiological investigations (INVEST).

Method: This was a parallel three-arm randomized single-blinded controlled trial, permitting two randomized comparisons: HTBF versus HT alone; INVEST- versus no-INVEST-guided intervention. The inclusion criteria were age 18–70 years; attending specialist hospitals in England; self-reported constipation for >6 months; refractory to basic treatment. The main exclusions were secondary constipation and previous experience of the trial interventions. The primary outcome was the mean change in Patient Assessment

of Constipation Quality of Life score at 6 months on intention to treat. The secondary outcomes were validated disease-specific and psychological questionnaires and cost-effectiveness (based on EQ-5D-5L).

Results: In all, 182 patients were randomized 3:3:2 (target 384): HT $n=68$; HTBF $n=68$; INVEST-guided treatment $n=46$. All interventions had similar reductions (improvement) in the primary outcome at 6 months (approximately −0.8 points of a 4-point scale) with no statistically significant difference between HT and HTBF (−0.03 points; 95% CI −0.33 to 0.27; $P=0.85$) or INVEST versus no-INVEST (0.22; −0.11 to 0.55; $P=0.19$). Secondary outcomes showed a benefit for all interventions with no evidence of greater cost-effectiveness of HTBF or INVEST compared with HT.

Conclusion: The results of the study at 6 months were inconclusive. However, with the caveat of under-recruitment and further attrition at 6 months, a simple, cheaper approach to intervention may be as clinically effective and more cost-effective than more complex and invasive approaches.

KEYWORDS
functional, gastroenterology, constipation, Randomised controlled trial, Biofeedback

INTRODUCTION

A proportion of patients with constipation (population 1%–2%) suffer chronic and disabling symptoms [1] and may be referred for specialist diagnostics and management, including habit training and biofeedback (HTBF). Termed chronic constipation (CC), first-line conservative treatments such as diet and lifestyle advice and laxatives frequently fail to address symptoms adequately in this group [2]. Hospital-based bowel re-training programmes, sometimes including focused biofeedback and psychosocial support, may therefore be trialled. A range of cohort studies [3], randomized controlled trials (RCTs) [4–9], reviews [10], guidelines [11] and a meta-analysis [12] attest to the general success of this approach. However, opinion varies greatly concerning the complexity of intervention required and UK survey evidence indicates that there is remarkable variability of practice [13]. More complex forms of therapy include instrument-based biofeedback learning techniques [3–9]. Favoured in the United States, and by about half of UK centres [13], these provide direct visual computer-based biofeedback of pelvic floor activity. While small RCTs suggest an additive value of biofeedback over habit training alone in the management of selected patient subgroups of CC, for example those with a 'functional defaecation disorder' (dyssynergic defaecation) [5, 14–16], there have been no multicentre or adequately powered RCTs in unselected patients despite the uncertainty having significant resource implications. Most publications advocating biofeedback have come from specialist centres with considerable 'investment' in these techniques with much less favourable reports when biofeedback is used as the disinvested comparator to a surgical intervention [17, 18].

The 2014 Cochrane Review 'Biofeedback for treatment of chronic idiopathic constipation in adults' [19] extracted efficacy data from 17 eligible RCTs including 931 participants. The authors considered 16 trials to be of high risk of bias. Inclusion criteria, notably CC versus defined 'functional defaecation disorder' (dyssynergic defaecation) and choice of outcome measure and comparator (standard care, sham biofeedback or range of alternative interventions including drugs and surgery) varied greatly between trials. Most trials had small sample sizes (median 60 participants [range 21–119]) and some, including the largest study (whose comparator was surgery) [18], had levels of attrition of up to 50% at primary outcome.

What does this paper add to the literature?

Biofeedback is well established in the pathway of care for patients suffering chronic constipation but evidence of benefit over and above habit training (HT) is lacking. The trial shows that the combination of biofeedback with HT and investigating patients before intervention (to guide treatment) both add cost without evidence of clinical benefit compared to HT alone.

The Cochrane Review concluded that there was 'insufficient evidence to allow any firm conclusions regarding the efficacy and safety of biofeedback for the management of people with CC' and a need for 'well-designed RCTs with adequate sample sizes, validated outcome measures (especially patient-reported outcome measures) and long-term follow-up'. The CapaCiTY (chronic constipation treatment pathway) I trial sought to address these gaps. This trial was part of a broader UK National Institute of Health Research funded research programme funded by the NIHR (PGfAR: RP-PG-0612-20001) [20]. The CapaCiTY programme addressed several questions pertinent to the development of a cost-conscious pathway of care to help reduce healthcare expenditures by appropriately sequencing the care

provided, while targeting more expensive therapies at those most likely to benefit.

The aims of the current study were (i) to determine whether standardized specialist-led habit training plus pelvic floor re-training using HTBF is more clinically effective than standardized specialist-led habit training alone (HT) at 6 months' follow-up; (ii) to determine whether outcomes of such specialist-led interventions are improved by stratification to HTBF or HT, based on prior knowledge of anorectal and colonic pathophysiology using standardized radiophysiological investigations (INVEST).

METHODS

Study design and participants

Trial objectives were addressed by a multicentre, parallel, three-arm, randomized trial design (Figure 1). In patients randomized to have investigations (INVEST arm), test results were used to stratify treatment intervention. This permitted two randomized comparisons: an overall evaluation of the performance of an INVEST panel in improving the selection of treatment and an evaluation of treatment options (HT vs. HTBF) without INVEST procedures. Thus, the overall evaluation addressed whether INVEST-guided care led to more favourable outcomes compared to randomized allocation. We recruited from 10 UK specialist centres that geographically encompass north–south England with a mix of urban and rural referral bases. Patients were recruited at the time of clinical consultation at physician and nurse-led clinics.

Baseline clinical evaluation

In addition to screening questions, clinical examination and information obtained by baseline questionnaire assessments (below), patients completed a structured interview to document other comorbidities and risk factors, for example 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 avoid unnecessary repetition of intimate examinations.

Inclusion and exclusion criteria

Chronic constipation was defined according to pragmatic criteria: broadly those employed for recent pivotal trials of prokinetics [21, 22] and UK guidance [23]. The main inclusion criteria were age 18–70 years; symptom onset >6 months prior to recruitment; symptoms met American College of Gastroenterology constipation definition [24]; constipation failed previous laxative and lifestyle treatment to a minimum basic standard [25]. The main exclusions were secondary constipation and previous experience of the interventions. Full details of inclusion and exclusion criteria are included in Data S1.

Procedures

Habit training, habit training + biofeedback and investigation protocols were standardized by prior consensus meetings and have been previously published in detail [26]. The content of the intervention is provided in Table S1 for convenience. In brief, HT was provided by a trained National Health Service (NHS) specialist (nurse or physiotherapist with clinical experience) who had undertaken a standard 1-day (study-specific) training session. A standardized approach and intervention were provided using an intervention manual. All participants were taught defaecation manoeuvres such as posture and breathing as well as addressing bowel routine, with individualized discussion of diet and fluids. Participants with evacuation difficulties or perineal descent were also taught pelvic floor muscle exercises. The course of therapy included three to four sessions (with interval tolerance of every 3–5 weeks). The first and last session were always face-to-face; intermediate sessions could be a telephone review. Sessions were delivered by the same therapist if possible and tailored to each participant's individual needs.

HTBF included the steps of HT but also included direct visual biofeedback using a portable high-resolution anorectal manometry catheter connected to a biofeedback computer monitor. Calibration, validation and maintenance of the equipment were built into the programme and training manuals were provided. Outcomes recorded over successive sessions included the ability to expel a rectal balloon, generate downwards propulsion of the balloon toward the anus, increase rectal pressure, relax the anal canal, and ability to sense the balloon at lower or higher volumes (relevant to hypo- and hyper-sensate patients).

Specialist INVEST were standardized nationally during development work based on a survey that showed universally discordant practice (no two UK centres had the same protocol for any of the five tests). Tests were only performed if they had not been carried out in the preceding 12 months and comprised high-resolution anorectal manometry; balloon sensory testing; fixed volume (50 mL) water-filled rectal balloon expulsion test; whole-gut transit study using radio-opaque markers; and X-ray barium defaecography. Full details of tests are provided in Table S2. Participants were given the results of investigations.

In patients randomized to have investigations (INVEST arm), results were used to stratify treatment intervention. Expert review of the combined test results was undertaken (by SMS and ST) to achieve a dichotomous conclusion of 'functional' defaecation disorder (FDD) versus no-FDD. On this basis, in this arm, patients were purposively allocated to HTBF if they had an FDD and to HT for no-FDD (other pathophysiological phenotypes).

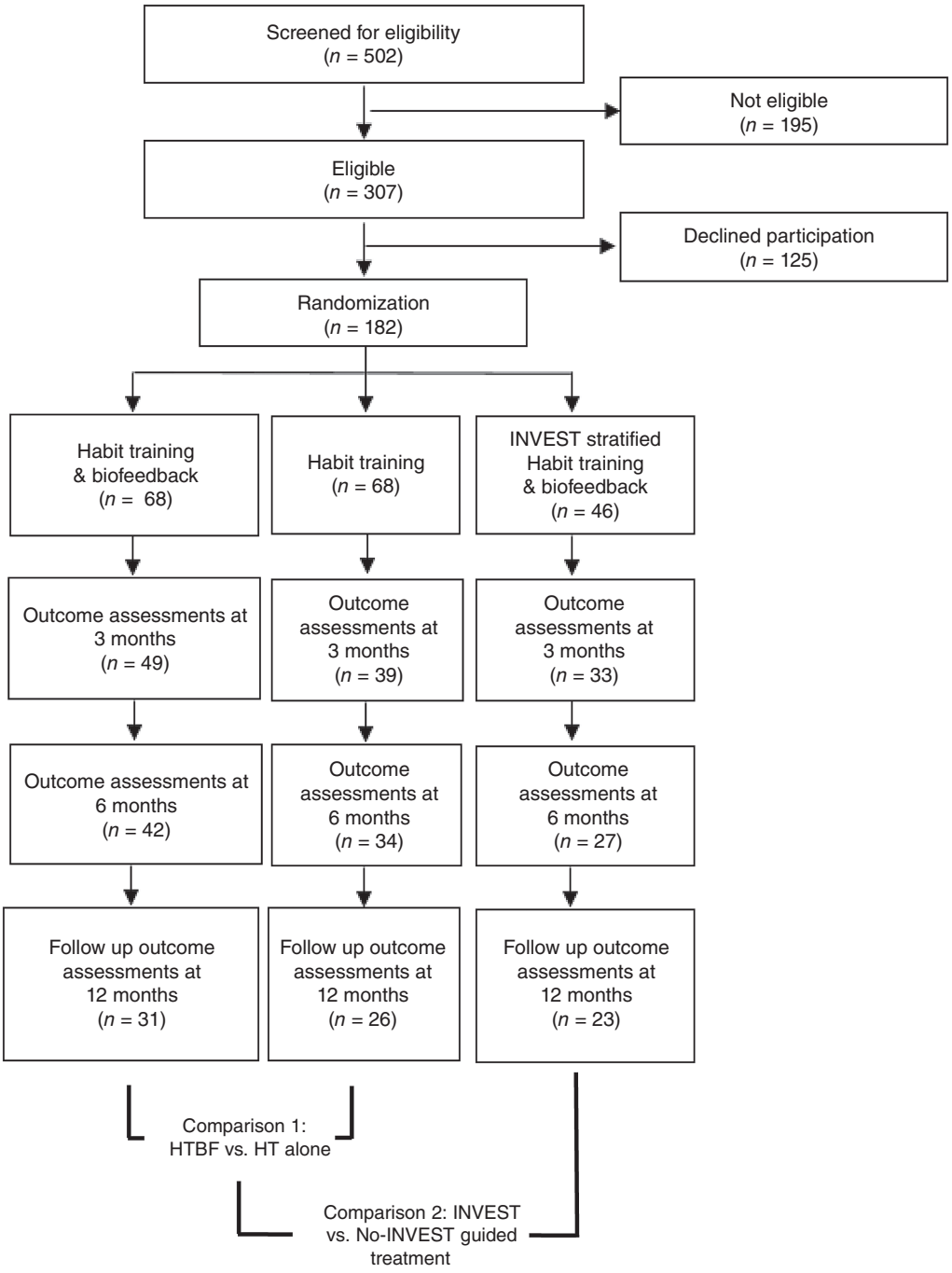

FIGURE 1 CONSORT flow diagram. Randomized allocation was based on a 3:3:2 ratio (HTBF:HT:INVEST stratified) as dictated by the sample size calculation. The design permitted two nested comparisons: (1) HTBF versus HT and (2) no-INVEST versus INVEST stratified treatment.

Outcome measures

A common standardized outcome framework was used throughout the CapaCiTY programme (three trials) [20]. All paper questionnaires were completed by the patient in an undisturbed environment without prompting at 0, 3, 6 and 12 months. Online and postal options were provided.

Primary clinical outcome

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 [27–29]. PAC-QoL includes 28 items covering four domains: each item is scored 0–4, and items and domains are aggregated to a composite

score (0–4). Minimum important point differences have been defined for PAC-QoL. Treatment effects have been characterized using cumulative distribution curves and a 1.0-point reduction has been confirmed as a robust measure of a responder [30]. Further, a minimum clinically important difference can be defined by a 10% change, that is, 0.4 points in the scale. Thus a 0.4 point (or greater) reduction in PAC-QoL was considered a minimally important mean difference between arms, at 6 months post-treatment.

Secondary outcomes

The secondary outcomes included several self-report instruments. These are detailed in Data S2 and tabulated in the Results section.

Health economic outcomes

Resource use at the patient level was captured using trial case report forms at scheduled clinical visits and contacts. Assessments were carried out at 0, 3, 6 and 12 months of follow-up, augmented by telephone calls. Patients' use of prescription drugs related to their condition was recorded and costed using Prescription Cost Analysis data [31]. Health service contacts were recorded by asking patients to recall general practitioner, district nurse, pharmacy, Accident and Emergency, outpatient and inpatient visits. Healthcare resource use was costed using published national reference costs. Individual patient costs were estimated in 2018 UK pounds sterling 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 [32], contributing to a broader societal costing (Table S3).

Generic health-related quality of life (QoL) was assessed using the EuroQol questionnaire consisting of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). EQ-5D-5L scores were converted to health status scores using the mapping function developed by van Hout et al. [33], providing a single health-related index including 0 (death) and 1 (perfect health), where negative scores are possible for some health states. Scores were captured within trial case report forms during clinic visits or contacts at baseline, 3, 6 and 12 months. Using the trapezoidal rule, the area under the curve (AUC) of health status scores was calculated, providing patient-level quality-adjusted life-year (QALY) estimates for the cost-effectiveness analyses. Since AUC estimates are predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates were adjusted for baseline scores within regression analyses.

Patient and health professional experience

Qualitative data were obtained to aid interpretation of outcomes and to aid development of an authoritative clinical pathway that recognized informational needs of both clinicians and patients. Face-to-face, digitally recorded, semi-structured interviews were conducted involving a purposive, diverse sample of patients and professionals, with participant recruitment reflecting a range of ages, geographical locations and where possible other pertinent attributes such as ethnicity and gender, continuing until data saturation when no new themes emerged. All participants were told that they might be invited for interview when they were informed about the trial but provided separate informed consent for interview (in those agreeing to be approached). A topic guide for interviews, informed by existing literature and patient advisors, was developed.

Adverse events

Adverse events were recorded throughout the trial using an adverse event log to record the nature, seriousness, causality, expectedness, severity, relatedness and outcome.

Sample size

Sample size was calculated using the primary clinical outcome, change in the PAC-QoL score. A 10% scale difference or 0.4-point reduction in the PAC-QoL score with a variance estimate conservatively set at SD = 1 was considered clinically relevant. To detect a mean change of 0.4 in the PAC-QoL score (SD = 1) with 90% power and 5% significance level, 132 per arm or 264 participants in total were required for the comparison of HT and HTBF (no-INVEST arm). For secondary comparison of INVEST versus no-INVEST a reduction of 0.4 points (SD = 1) was also considered clinically meaningful. To detect an effect size of 0.4 with 90% power and at a 5% significance level required 90 participants in the INVEST arm assuming 264 participants were recruited to the no-INVEST arm (leading to the 3:3:2 allocation ratio). Allowing for 10% loss to follow-up, a sample size of 147 was needed in both the HT and HTBF arms and 100 in the INVEST arm. A total sample size of 394 patients across the three arms was required.

Interim analyses and stopping guidelines

There were none.

Randomization and masking

Randomization (HT, HTBF, INVEST; allocation ratio 3:3:2) was delivered at one point in time following recruitment (after eligibility and baseline assessments). Randomization was stratified by sex (and women also by centre) with block (block size 8) randomization implemented via an online randomization system developed by the Pragmatic Clinical Trials Unit (PCTU) to ensure allocation concealment. Randomization was conducted by suitably trained and delegated researchers at recruiting sites and followed PCTU-validated standard operating procedures for the study.

Patients and clinicians were necessarily aware of both INVEST and treatment allocations. To minimize 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 an opaque envelope. Participants were trained in completing questionnaires prior to randomization and received a visual aid with standardized script and training for completing questionnaires.

Statistical analysis

The primary outcome was analysed on an intention-to-treat basis at the 6-month time point. Descriptive statistics are presented (i.e., mean, standard deviation, median and interquartile range) by trial arm. The PAC-QoL score at 6 months was compared between trial arms using a mixed regression model with study site as a random effect, adjusting for baseline PAC-QoL score, gender and breakthrough medication (use of oral and/or rectal laxatives). Adjustment was pre-specified in the analysis plan. Adjustment for stratification factors (in this case site and gender), baseline outcome and other known prognostic factors improves precision even when those factors are balanced, and is in line with published guidance [34, 35]. In the case of partially completed questionnaires, simple imputation was used in instances where more than half the items were completed by a participant (e.g., 14 or more of the 28 items in the PAC-QoL), so that we did not need to discard the whole questionnaire.

Secondary outcomes were also analysed on intention to treat and presented as descriptive statistics by trial arm: continuous variables (e.g., PAC-QoL score) were summarized by treatment group using mean, standard deviation, median and interquartile range; for categorical variables, numbers and percentages of patients reporting each response option are presented by trial arm. Given the much less than target number of patients recruited to the trial, it was agreed that adjusted analysis would only be performed on selected secondary outcomes (i.e., PAC-QoL scores) with unadjusted treatment differences and respective 95% confidence intervals for other secondary outcomes. Results obtained using the CC behavioural response to illness questionnaire and Brief Illness Perception questionnaire have been omitted and will be reported separately.

The three-way cost-effectiveness comparison required the presentation of the cost-effectiveness acceptability frontier, as the cost-effectiveness acceptability frontier correctly identifies the optimal decision across the range of willingness-to-pay (WTP) when more than two options are being considered. 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.

Patient and public involvement

A Constipation Research Advisory Group (CRAG) comprised eight patients and two carers from London and Durham. This group had geographical diversity (north and south) and a disease-appropriate demographic (eight women, two men). Patient and public involvement (PPI) was managed by two patient co-applicants and the CRAG had an active 'contributory' rather than 'representative' role. The over-arching functions of the CRAG included steering/advisory group participation, development of participant information resources and advice on protocol revisions.

Role of the funding source

The funder of this study had no role in the design, data collection, data analysis, interpretation or writing of the report.

RESULTS

Participants

Recruitment started on 26 March 2015 (first intervention 21 May 2015) and ended 30 June 2018. A total of 182 (of target 394) patients were randomized of 502 screened (36.3%) from 10 sites. Two sites opened but failed to recruit; the remainder randomized between seven and 71 patients. Reasons for screen failures are shown in Figure S1. The most common reasons were that HT or biofeedback had previously been used (39%) or that patients were naïve to basic diet and lifestyle and laxative interventions (14%). Sixty-eight patients were randomized to HT, 68 to HTBF, and 46 underwent INVEST-guided therapy (HT or HTBF based on the results of investigations) (Figure 1). Table 1 provides main baseline characteristics presented by trial arm (full data, Table S4).

Primary outcome

In all, 178 patients provided PAC-QoL data at one or more time points (Figure 2). The primary outcome (PAC-QoL) was available at both baseline and 6 months for only 90 patients. Scores were improved in all three arms but with no statistically significant differences between arms. There was no evidence of an additive effect of HTBF over and above HT alone ($P = 0.84$) and no evidence of a difference between INVEST and no-INVEST (confidence interval −0.11 to 0.55, $P = 0.19$) (Table 2). Note that the denominators in the table differ from the flowchart as some patients remained in the study but failed to fully complete the primary outcome measure.

Secondary outcomes

Table S5 shows changes in PAC-QoL scores analysed as binary variables (adjusted analyses). Secondary clinical outcomes at 6 months are shown in Table 3. Other time points are shown in Table S6.

TABLE 1 Demographic and clinical characteristics of patients randomized.

	HT ($n=68$)	HTBF ($n=68$)	Total number INVEST[a] ($n=136$)	INVEST ($n=46$)	Total ($n=182$)
Referral source, no. (%)					
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, no. (%)	1 (1.5)	1 (1.5)	2 (1.5)	1 (2.2)	3 (1.6)
Demographic characteristics					
Gender, no. (%)					
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, no. (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Ethnicity, no. (%)					
White	48 (70.6)	49 (72.1)	97 (71.3)	33 (71.7)	130 (71.4)
Black	7 (10.3)	8 (11.8)	15 (11.0)	5 (10.9)	20 (11.0)
Asian	11 (16.2)	10 (14.7)	21 (15.4)	5 (10.9)	26 (14.3)
Mixed	1 (1.5)	0 (0.0)	1 (0.7)	2 (4.3)	3 (1.6)
Other	1 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)
Missing, no. (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Age					
Mean (SD)	45.2 (13.6)	45.7 (15.6)	45.4 (14.6)	43.6 (12.2)	45.0 (14.0)
Median (interquartile range)	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, no. (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Past obstetric history (women only), no. (%)	38 (63.3)	37 (62.7)	75 (63.0)	27 (69.2)	102 (64.6)
No. 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)
No. of caesareans, mean (SD)	0.2 (0.5)	0.4 (0.6)	0.3 (0.6)	0.4 (0.8)	0.3 (0.6)
No. of forceps/ventouse, mean (SD)	0.1 (0.3)	0.2 (0.4)	0.2 (0.4)	0.1 (0.6)	0.1 (0.4)
No. of episiotomies, mean (SD)	0.5 (0.8)	0.4 (0.8)	0.4 (0.8)	0.6 (0.7)	0.5 (0.8)
No. 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, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Faecal incontinence symptoms, no. (%)	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)
Post defaecation leakage	10 (14.7)	10 (14.7)	20 (14.7)	15 (32.6)	35 (19.2)
Difficulty in wiping clean	24 (35.3)	16 (23.5)	40 (29.4)	24 (52.2)	64 (35.2)
Missing, no. (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Pelvic organ prolapse symptoms, no. (%)	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)

(Continues)

TABLE 1 (Continued)

	HT ($n=68$)	HTBF ($n=68$)	Total number INVEST[a] ($n=136$)	INVEST ($n=46$)	Total ($n=182$)
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, no. (%)	0 (0.0)	1 (1.5)	1 (0.7)	2 (4.3)	3 (1.6)
Urinary symptoms, no. (%)	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, no. (%)	0 (0.0)	1 (1.5)	1 (0.7)	1 (2.2)	2 (1.1)
Joint hypermobility, no. (%)	17 (25.0)	15 (22.1)	32 (23.5)	12 (26.1)	44 (24.2)
Missing, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PAC-QoL					
Mean (SD)	2.34 (0.74)	2.37 (0.85)	2.35 (0.80)	2.54 (0.77)	2.40 (0.79)
Missing, no. (%)	0 (0.0)	2 (2.9)	2 (1.5)	2 (4.5)	4 (2.2)

Note: Hypermobility was indicated by a response of "yes" to two or more questions out of five used to assess joint hypermobility.

Abbreviations: HT, habit training; HTBF, habit training biofeedback; INVEST, radio-physiological investigations; PAC-QoL, Patient Assessment of Constipation Quality of Life.

[a]HT and HTBF arms together form the no-INVEST arm.

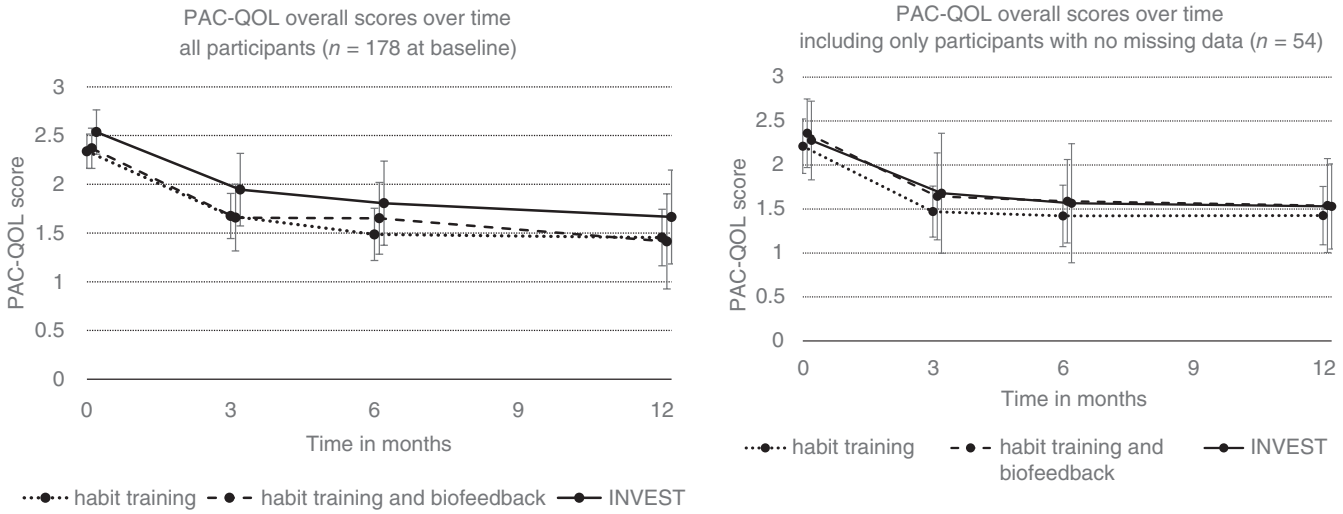

FIGURE 2 Mean PAC-QoL scores over time. Error bars show 95% confidence intervals.

TABLE 2 PAC-QoL scores by randomized 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.

	Mean score at 6 months (SD)				
	HT ($n=38$)	HTBF ($n=30$)		Adjusted mean difference[a] (95% confidence interval)	*P* value
HT vs. HTBF	1.49 (0.85)	1.65 (1.03)		−0.03 (−0.33, 0.27)	0.844
	No-INVEST (HT or HTBF) ($n=68$)		INVEST ($n=22$)		
No-INVEST vs. INVEST	1.56 (0.93)		1.81 (1.03)	0.22 (−0.11, 0.55)	0.187

Abbreviations: HT, habit training; HTBF, habit training with direct visual biofeedback; INVEST, radio-physiological investigations; PAC-QoL, Patient Assessment of Constipation Quality of Life.

[a]Adjusted for gender, site, baseline PAC-QoL score, and breakthrough medication (i.e., use of oral and/or rectal laxatives), as described in the Methods.

TABLE 3 Secondary outcome scores at 6 months by randomized group for other continuous secondary outcomes, 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.

Continuous outcomes	*n*	Baseline mean (SD)	Follow-up mean (SD)	Treatment difference (95% confidence interval)
PAC-SYM score, overall				
HT	38	2.2 (0.8)	1.5 (0.8)	Reference
HTBF	30	2.1 (0.8)	1.5 (1.1)	−0.1 (−0.5, 0.3)
No-INVEST	68	2.1 (0.8)	1.5 (0.9)	Reference
INVEST	22	2.2 (0.9)	1.7 (0.8)	−0.2 (−0.6, 0.2)
PAC-SYM score, stool symptoms				
HT	38	2.5 (0.9)	1.8 (1.0)	Reference
HTBF	30	2.5 (0.9)	1.7 (1.3)	0.1 (−0.4, 0.6)
No-INVEST	68	2.5 (0.9)	1.8 (1.1)	Reference
INVEST	22	2.6 (1.0)	2.0 (1.0)	−0.3 (−0.8, 0.2)
PAC-SYM score, abdominal symptoms				
HT	38	2.2 (0.9)	1.3 (0.9)	Reference
HTBF	30	2.0 (1.0)	1.5 (1.2)	−0.2 (−0.7, 0.3)
No-INVEST	68	2.1 (1.0)	1.4 (1.0)	Reference
INVEST	22	2.0 (1.1)	1.7 (1.0)	−0.3 (−0.8, 0.2)
PAC-SYM score, rectal symptoms				
HT	37	1.5 (1.1)	1.0 (0.8)	Reference
HTBF	30	1.6 (1.1)	1.2 (1.2)	−0.2 (−0.7, 0.3)
No-INVEST	67	1.5 (1.1)	1.1 (1.0)	Reference
INVEST	22	1.7 (1.3)	1.1 (0.9)	0.0 (−0.5, 0.5)
Diary data, bowel frequency—mean number of attempts to empty bowels over 2 weeks				
HT	34	29.0 (24.1)	21.8 (11.0)	Reference
HTBF	29	26.6 (18.1)	22.6 (13.8)	−0.7 (−7.0, 5.6)
No-INVEST	63	27.9 (21.4)	22.2 (12.3)	Reference
INVEST	22	28.4 (15.6)	23.0 (11.5)	−0.8 (−6.8, 5.2)
Diary data, bowel frequency—mean number of times stool was actually passed over 2 weeks				
HT	34	15.8 (11.7)	14.2 (8.3)	Reference
HTBF	28	14.8 (8.9)	15.4 (11.3)	−1.2 (−6.2, 3.8)
No-INVEST	62	15.3 (10.4)	14.8 (9.7)	Reference
INVEST	22	13.8 (7.7)	14.3 (8.2)	0.5 (−4.1, 5.1)
Diary data, nature of bowel movement—mean number of days laxatives used out of 14				
HT	34	3.6 (4.5)	0.5 (1.6)	Reference
HTBF	29	3.5 (4.8)	1.0 (2.7)	−0.4 (−1.5, 0.7)
No-INVEST	63	3.5 (4.6)	0.7 (2.2)	Reference
INVEST	22	6.2 (6.1)	0.6 (3.0)	0.1 (−1.1, 1.3)
Diary data, nature of bowel movement—mean number of days glycerine suppositories used out of 14				
HT	34	0.2 (0.7)	0.8 (2.0)	Reference
HTBF	29	0.9 (2.1)	1.2 (2.8)	−0.4 (−1.6, 0.8)
No-INVEST	63	0.5 (1.5)	1.0 (2.4)	Reference
INVEST	22	1.3 (3.6)	1.2 (3.1)	−0.3 (−1.6, 1.0)
EQ VAS scores				
HT	39	69.9 (19.7)	69.0 (23.8)	Reference
HTBF	29	66.1 (20.1)	71.0 (20.1)	−2.0 (−12.9, 8.9)
No-INVEST	68	68.3 (19.8)	69.8 (22.1)	Reference
INVEST	22	68.1 (16.6)	71.1 (17.3)	−1.3 (−11.6, 9.0)

(Continues)

TABLE 3 (Continued)

Continuous outcomes	*n*	Baseline mean (SD)	Follow-up mean (SD)	Treatment difference (95% confidence interval)
PHQ 9				
HT	38	7.5 (6.5)	7.7 (7.4)	Reference
HTBF	30	6.8 (6.4)	7.2 (6.9)	0.5 (−3.0, 4.0)
No-INVEST	68	7.2 (6.4)	7.5 (7.1)	Reference
INVEST	22	8.8 (4.8)	8.8 (5.6)	−1.4 (−4.7, 1.9)
GAD 7 (anxiety)				
HT	38	6.9 (6.4)	5.8 (6.3)	Reference
HTBF	30	7.0 (6.4)	6.4 (6.0)	−0.6 (−3.6, 2.4)
No-INVEST	68	7.0 (6.4)	6.1 (6.1)	Reference
INVEST	22	8.4 (6.0)	8.7 (6.4)	−2.6 (−5.6, 0.4)
Global patient satisfaction score				
HT	37	—	2.8 (0.9)	Reference
HTBF	29	—	2.3 (1.3)	0.4 (−0.1, 0.9)
No-INVEST	66	—	2.6 (1.1)	Reference
INVEST	21	—	2.5 (1.1)	0.1 (−0.4, 0.6)
Global patient improvement score				
HT	38	—	65.8 (23.1)	Reference
HTBF	28	—	52.7 (35.2)	13.0 (−1.4, 27.4)
No-INVEST	66	—	60.2 (29.4)	Reference
INVEST	22	—	45.7 (30.2)	14.5 (0.0, 29.0)

Abbreviations: EQ VAS, EQ visual analogue scale; GAD 7, Generalized Anxiety Disorder 7-item; HT, habit training; HTBF, habit training biofeedback; INVEST, radio-physiological investigations; PAC-SYM, Patient Assessment of Constipation Symptoms; PHQ 9, Patient Health Questionnaire-9.

Secondary outcomes covering symptoms and QoL improved for both HT and HTBF, for example Patient Assessment of Constipation Symptoms (PAC-SYM) reduced (improved) from 2.2 at baseline to 1.5 at 6 months; weekly laxative use reduced fourfold. Interventions led to small reductions in depression but there were no significant differences between intervention arms. Overall, about 65% patients were globally satisfied or very satisfied with both interventions.

Cost-effectiveness

Given similar changes in EQ-5D-5L for all interventions, cost-effectiveness analyses favoured the least expensive interventions, that is, HT and no-INVEST, as the dominant strategy. In both instances cost increases were significant (HTBF vs. HT £239, 95% CI 133–354; INVEST vs. HT £543, 95% CI 403–685), while QoL reduced marginally compared to HT: HTBF (−0.010 QALYs, 95% CI −0.053 to 0.03); INVEST (−0.047 QALYs, 95% CI −0.093 to −0.001). The probability that HT is cost-effective was $P = 0.83$ at WTP £30 000/QALY, compared to HTBF or INVEST alternatives. Full cost-effectiveness analyses with tables and figures are included in the published NIHR report [20].

Patient and health professional experience

Findings from quantitative clinical outcomes (HT vs. HTBF) were reflected by patient experience reported at interview, that is, similar proportions of patients liked (and a minority disliked) both interventions for several reasons. Similar results were obtained for the INVEST versus no-INVEST comparison. Patients provided reasons for liking INVEST, for example greater knowledge of their condition (and knowing that this was not 'all in their mind') versus disliking the invasiveness and embarrassment of the tests. A more complete description is found in Data S3. Staff were generally supportive, but some found adhering to the agreed intervention protocol constrained their clinical flexibility and would have preferred to individualize the intervention. The biofeedback element added time to consultations, or limited what they could cover in HT. More detailed results are reported elsewhere [20].

Adverse events

There were only two serious adverse events. Both were unexpected and were in the INVEST arm. Both required either hospitalization or prolongation of existing hospitalization. Neither was

judged as being related to treatment. One patient withdrew from the study; the other did not. A full table of adverse events is provided in Table S7.

DISCUSSION

Main findings

Included adults with CC had a high symptom burden and long duration 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. In this patient group, analysis of clinical effectiveness showed that all interventions trialled (HT or HTBF with or without INVEST) reduced symptom burden and improved disease-specific QoL. The observed magnitude of these changes (approximately 0.8 points in PAC-QoL) can be considered as clinically meaningful and represented a greater reduction than the minimum important difference sought between groups by design (mean change of 0.4 points). These findings from the primary outcome were consistent with a panel of secondary outcomes, such as QoL and laxative use (which reduced fourfold), which improved with both HT and HTBF. While such improvements are unlikely to have occurred spontaneously with time for a condition that is generally considered chronic and stable, it is acknowledged that the observed attrition rates in both study arms, if reflecting dissatisfaction with treatment, could have artificially inflated effect sizes. Regardless, while all interventions had an effect, confidence intervals rule out a clinically important difference between HT and HTBF for the primary outcome and for all main secondary outcomes. The addition of stratified therapy by use of INVEST did not confer any significant benefit over randomized allocation (no-INVEST). All procedures were safe and well tolerated by patients. While all conclusions must be tempered with the major caveat of under-recruitment leading to under-powering of quantitative results, these findings have potential to influence clinical care.

Health economic analyses demonstrated strong support for HT and no-INVEST based on cost-effectiveness analyses. Despite under-recruitment (182 of a planned 394), patient-level data provide 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 (pelvic floor re-training using biofeedback) nor stratification to complex or standardized therapy based on prior knowledge of anorectal and colonic pathophysiology (INVEST) were more cost-effective than standardized specialist-led HT. Analysis suggests that standardized HT is the dominant strategy (lower cost, greater QoL) at a WTP of £30 000/QALY.

Interviews suggested patient experience was mixed. Some regretted not being allocated to INVEST or HTBF (because they believed they would have less knowledge of their condition and less likelihood of treatment success), while others felt that the tests and biofeedback were embarrassing and intrusive. Most reported a positive interaction with staff and at least some symptom benefit and would recommend trying the intervention they received to other people with CC.

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, that is, HT without INVEST. This is an important finding, especially for the utility of INVEST. These take time in treatment pathways that may already be delayed by resource constraints as well as adding to cost. There is also concern that some radiological investigations, especially defaecography, can over-focus the patient on dynamic structural abnormalities, for example small rectoceles and degrees of internal prolapse that are not considered clinically significant and which may incline the patient toward ill-advised surgery [36].

Limitations

The programme was severely hampered by poor recruitment and poor retention of participants. 182 patients were randomized representing less than half of the predetermined sample size, and the primary outcome could only be derived for 90 participants. Even after simplifying the trial design at the award approval stages, and significant PPI input, the study was probably over-ambitious in design and could have benefitted from more pragmatism at inclusion, intervention and follow-up stages. Other barriers to delivery that were less directly related to design are discussed in the full published report [20].

We had not anticipated the recruitment and retention difficulties we encountered and did not have ethical approval to approach those eligible but not recruited nor those who dropped out to determine reasons. The only light we can cast upon this is anecdotal from staff interviews, where some expressed the opinion that some participants wanted the 'full' biofeedback intervention (many had been referred to the clinics for this) and some did not attend for follow-up appointments as their symptoms were improved. We cannot verify this.

Despite under-recruitment and poor retention, it is important to publish these data as the trial was publicly funded and the information we have collected may inform future studies. We obviously set out to conduct a fully powered study with a longer follow-up, but our steering committee decided to cut short the follow-up period at 6 months due to poor recruitment and retention rates. Future studies would benefit from a much longer follow-up.

Comparison with previous studies

Of previous trials, the 2006 trial of Chiarioni and colleagues [9] is most similar in design to the current trial. 109 patients with constipation underwent five sessions of electromyography biofeedback versus optimized medical management, counselling and education. Biofeedback was found to be superior at both 6 and 12 months:

80% (43/54) of biofeedback patients reported clinical improvement compared to 22% (12/55) laxative-treated patients (relative risk (RR) 3.65, 95% CI 2.17–6.13). This study included only patients with pelvic floor dyssynergia. While CapaCiTY I included patients with mixed pathophysiology in the trial as a whole, the INVEST arm did select patients with proven FDD (on at least two diagnostic tests) for HTBF, showing now benefit over and above HT.

Only two other trials have compared biofeedback with forms of conventional supportive (non-drug, non-surgical) treatment. Hu et al. [37] randomized 60 patients with CC to two groups: 30 patients underwent biofeedback incorporating balloon expulsion versus 30 who received lifestyle, dietary and general advice only (HT). The number of spontaneous bowel movements increased in both groups. There was a decrease in bloating, incomplete evacuation, straining and rescue laxative use in the biofeedback group but not in the control group (abstract publication only). Simon and Bueno [16] randomized only 30 elderly patients to electromyography biofeedback versus advice and counselling, reporting a statistically significant difference between biofeedback and control in the frequency of defaecations per week. The current trial results differed from these studies in the high response in the comparison group to intervention, that is, HT was comparable to the HTBF group. This could reflect our inclusion of a patient cohort with significant psychological comorbidity that thus responded favourably to the intensive support provided to both groups. Alternatively, it could reflect the attention paid to limit bias that might have favoured the active intervention in previous studies [19]. It is also possible to combine habit training or biofeedback with other conservative interventions such as, for example, suppositories [38]. Finally, our results could reflect our failure to specifically select patients with dyssynergia for the trial. This is controversial in respect of previous trial data and in the methods used to determine whether a patient has dyssynergia in the first place [39, 40]. Since our study was planned, one RCT has reported on home biofeedback compared to office biofeedback for dyssynergic defaecation and found home therapy was not inferior; both improved QoL and home treatment was more cost-effective [41].

Despite under-recruitment, the current RCT is still the largest to date where biofeedback is one of the trialled interventions for constipation. It is therefore acknowledged that, amongst many UK practitioners, there will be a sentiment that the results do still answer a major question—namely whether the sort of specialist-led biofeedback practice advocated by some expert centres (predominantly in the United States) is less likely to work in an NHS pathway. There is a general scepticism (reinforced by the findings of the prior Cochrane Review [19]) that direct visual biofeedback offers little to patients over and above the panoply of approaches embodied within habit training (including holistic elements of patient support as well as didactic training). This may be an issue of comparing like with like—thus the 'average' UK NHS patient with severe long-lasting symptoms and psychological comorbidity (as in the current trial) might not respond in the same way to carefully selected patients with dyssynergia attending clinics in the United States. The Chiarioni trial [9] included a homogeneous cohort of dyssynergic patients with age 34 ± 1.5 years compared to 45 (SD 14) years in the current trial. Similarly, it is possible that the highly focused specialist practice of some biofeedback advocates delivers a quality of therapy that is superior to that delivered by multiple practitioners across centres in the UK. In the Chiarioni study [9], a single senior gastroenterologist provided all treatments. Whether this is important or not, such delivery would not be feasible in the UK NHS.

It is the authors' view that the identical outcome effect size for all arms of the current study implies that a future trial, even of very much greater sample size, would be unlikely to detect a clinically important difference between interventions. Certainly, the confidence interval for the effect comparing HT and HTBF excludes the difference we initially set as the minimum clinically important difference in our sample size calculation. It is thus hard to recommend further investment, even in a more simplified trial design. There is evidence that psychological treatments such as cognitive behavioural therapy have significant and sustained benefit on symptoms, mood and QoL in people with irritable bowel syndrome (many of whom also experience severe constipation) and future work could focus rather on use of psychological methods alongside HT [42, 43].

CONCLUSIONS

Firm conclusions are limited by significant under-recruitment and attrition. However, synthesis of clinical and cost-effectiveness data with qualitative experience provides themes. In unselected CC patients HT helps the majority, and the more costly, time-consuming and invasive intervention of HTBF should not be considered first-line. Expensive and invasive INVEST cannot be recommended as a first step in the care pathway. Future interventions should focus on incorporating psychological methods alongside HT to address psychological comorbidity.

AUTHOR CONTRIBUTIONS

Christine Norton: Conceptualization; funding acquisition; writing – original draft; writing – review and editing. **Sybil Bannister:** Investigation; data curation; project administration. **Lesley Booth:** Investigation; writing – review and editing. **Steve R. Brown:** Writing – review and editing; funding acquisition. **Samantha Cross:** Formal analysis; writing – review and editing. **Sandra Eldridge:** Conceptualization; formal analysis; funding acquisition; writing – original draft; writing – review and editing; methodology; project administration; data curation. **Christopher Emmett:** Writing – original draft; writing – review and editing. **Ugo Grossi:** Writing – original draft; writing – review and editing; project administration; investigation. **Mary Jordan:** Formal analysis; writing – original draft; writing – review and editing. **Jon Lacy-Colson:** Funding acquisition; writing – original draft; writing – review and editing. **James Mason:** Conceptualization; formal analysis; funding acquisition; writing – original draft; methodology; supervision; writing – review and editing. **John McLaughlin:** Supervision; writing – original draft; writing – review and editing; project administration.

Rona Moss-Morris: Conceptualization; funding acquisition; writing – original draft; writing – review and editing; methodology. **S. Mark Scott:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; writing – review and editing; supervision. **Natasha Stevens:** Investigation; project administration; writing – original draft; data curation; writing – review and editing. **Shiva Taheri:** Investigation; project administration; writing – original draft; writing – review and editing; data curation. **Stuart A. Taylor:** Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; methodology. **Yan Yiannakou:** Conceptualization; funding acquisition; writing – original draft; writing – review and editing; methodology. **Charles H. Knowles:** Conceptualization; investigation; funding acquisition; project administration; writing – original draft; methodology; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Christine Norton: has received lecture fees from Takeda and Janssen Pharmaceuticals, unrelated to this work. Sybil Bannister, Lesley Booth, Steve R. Brown, Samantha Cross, Christopher Emmett, Ugo Grossi, Mary Jordan, James Mason, John McLaughlin, Natasha Stevens and Shiva Taheri: none. Sandra Eldridge: was a member of NIHR PGfAR board, NIHR HTA board, NIHR CTU standing advisory board, and reviewer for NIHR COVID-19 Urgent Public Health Board during the course of the programme. Jon Lacy-Colson was a paid consultant to Origin Sciences during the course of the programme (but on unrelated research area). Rona Moss-Morris reports personal fees from ad hoc payments for workshop therapist training in CBT for irritable bowel syndrome (a related syndrome), personal fees from consultancy payments from Mahana therapeutics and is a beneficiary of a licence agreement between King's College London and Mahana Therapeutics for a digital version of CBT for irritable bowel syndrome. S. Mark Scott received honoraria from Laborie for teaching during the programme (unrelated). Stuart A. Taylor: shareholder in Motilent unrelated to the work; research consultant to AstraZeneca unrelated to the work. Yan Yiannakou was in receipt of a grant from McGregor during the programme, unrelated to this work. Charles H. Knowles was a paid consultant to Medtronic during the programme (but on an unrelated research area).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by an NHS ethics committee (reference 14/LO/1786).

PATIENT CONSENT STATEMENT

All participants signed a consent form before being enrolled and randomized into the study.

CLINICAL TRIAL REGISTRATION

This study was registered as ISRCTN 11791740.

PROTOCOL

The full protocol for this study can be found in the published paper [20].

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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