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RESEARCH

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Clinical and cost effectiveness of nurse led-structured management of diarrhoea predominant irritable bowel syndrome in primary care (Lincolnshire POACHER study); a randomised control trial

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Abstract

Background Irritable Bowel Syndrome (IBS) is common and impairs quality of life. IBS is usually diagnosed using symptom-based criteria. Treatment leads to remission in < 50%.

Methods A randomised controlled trial was conducted in primary care to evaluate whether patients meeting Rome IV criteria for diarrhoea-predominant irritable bowel syndrome (IBS), presenting to primary, care benefit from a stepwise investigative approach with treatments tailored to alternative diagnoses. Participants were randomised 1:1 to management by general practitioners encouraged to follow National Institute of Health Care Excellence IBS Guidelines (controls) or structured investigation and treatment of newly diagnosed conditions (intervention). The primary end point was IBS Symptom Severity Score (IBSSSS) change.

Results Between October 2020- September 2023, 113 participants 81 female, mean age 36 years, 62 (70%) with severe symptoms, from 44 Lincolnshire practices were randomised, of whom 81 completed follow-up (28% attrition). Study arms were balanced. Mean IBSSSS (SD) decreased from 303.00 (92.85) to 234.05 (114.20) in the control arm and from 312.00 (72.59) to 126.49 (85.26) in the intervention arm. The absolute adjusted between-group mean difference was - 112.29 points (95% CI -151.68 to -72.91; $p < 0.0001$), corresponding to a large standardised effect size (Hedges' $g = 0.95$). Improved quality of life ($p < 0.001$) and anxiety ($p = 0.04$) also favoured intervention.

In 74% ($n = 32/43$) of intervention participants completing the study, appropriate treatment of alternative diagnoses was reported to lead to sustained clinical improvement. Diagnoses included bile acid diarrhoea ($n = 18$, 42%), small intestinal bacterial overgrowth ($n = 13$, 30%), fructose intolerance ($n = 8$, 19%), exocrine pancreatic insufficiency ($n = 3$, 7%), lactose intolerance ($n = 2$, 5%) and coeliac disease ($n = 1$, 2%) with more than one condition in 12 participants

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(28%). Advice on lifestyle (n=13, 30%) and toileting (n=15, 35%) provided additional sustained benefit. Mean intervention costs were £1396 compared to £315 for controls. The number of appointments did not correlate with final IBSSSS (p=0.21).

Conclusions Despite significant findings, under-recruitment, higher-than-anticipated loss to follow-up and lack of blinding may overestimate the benefits found (prospective trial registration: 14th July 2020, ISRCTN87945798).

Key Message

What is already known on this topic.

Irritable Bowel Syndrome (IBS) is the most common gastrointestinal condition seen by primary care. IBS characterised by diarrhoea (IBS-D), when treated following NICE guidelines recommended for Primary Care, has a remission rate <50% at 7 years. NICE guidelines advocate a positive diagnosis should be made if there are no red flag symptoms, typical symptoms and specified blood tests are normal. However, other data suggest that accurate diagnosis of disorders mimicking IBS-D require a different approach. No randomised studies have previously investigated the benefit from a more detailed testing strategy in this patient group presenting to primary care.

What this study adds

This trial suggests that there may be clinical benefit from lifestyle assessment combined with a structured investigative approach, compared to normal care. Appropriate investigations and treatment can be delivered by trained nurses. Currently, NICE guidelines in this patient group are frequently disregarded by GPs.

How this study might affect research, practice or policy

NICE Guidance to GPs does not reflect the approach advocated by the British Society of Gastroenterology when these patients present to secondary care. More research is needed to assess which investigations are valuable, the best sequence of investigations, and how these can be introduced in primary care.

Keywords Irritable Bowel Syndrome, Randomised trial, Defaecation, Diarrhoea, Bloating, Flatulence, Pain, Bile acid diarrhoea, Small intestinal bacterial overgrowth, Pancreatic insufficiency, Fructose intolerance, Endoscopy, Quality of life, Health economics, Primary care, Incremental Cost Effectiveness Ratio, ICER, QALY

Introduction

Irritable Bowel syndrome (IBS) is a chronic condition in which abdominal discomfort is associated with a change in bowel habit. Patients diagnosed with IBS have a significantly decreased health-related quality of life [1]. They have higher healthcare costs and lower work productivity than those without IBS [2]. The annual direct healthcare costs of IBS in the United Kingdom are estimated to be £1.3-2 billion [3].

IBS affects 5–10% of the world's population [4]. The aetiology of IBS is not understood, however, the psychological co-morbidity associated with IBS, the increased prevalence of anxiety and depression in sufferers has promoted research investigating disorder of the gut brain axis. To date, benefits from this research have been modest [5].

IBS is not diagnosed using objective criteria. Instead, it is recommended that IBS can be diagnosed if specific symptoms are present, there are no worrying features and physical examination and simple investigations are normal [6]. While recommendations vary as to which investigations are appropriate, wide-ranging investigations are discouraged although only two randomised trials in secondary care, limited in scope, have ever assessed which investigations are helpful. One focused on measuring faecal calprotectin levels [7], the other on the benefit of flexible sigmoidoscopy [8]. There have been no

randomised studies in primary or secondary care that have examined whether a more comprehensive investigational approach, with the potential to identify functional disorders undetectable by blood tests, calprotectin levels and sigmoidoscopy, has any merit.

There are three major reasons to question why it is adequate to diagnose IBS using only symptom-based criteria and a narrow spectrum of tests. First, symptom-based criteria identify organic disorders inaccurately [9], secondly, studies show that alternative pathologies mimic the symptoms of IBS especially when the IBS is characterised by diarrhoea [10] and thirdly, when a symptom based approach and recommended treatments are used, in the majority of sufferers, symptoms continue [11].

This two-arm parallel randomised controlled trial (RCT) therefore, was designed to investigate whether patients who meet symptom-based criteria for IBS, characterised by diarrhoea, presenting to primary care, benefit from an ordered, investigative approach with treatments tailored to any alternative condition(s) diagnosed. Mindful of the number of these patients and the burden from additional investigations, we trained nurses to investigate and manage trial participants randomised to the intervention arm. Our intervention was compared to real life management by general practitioners (GP) asked to bear in mind the United Kingdom (UK) National

Institute of Health and Care Excellence (NICE) recommendations [11].

Methods

The Lincolnshire Poacher study (Promoting Optimal Assessment to Change Health and Engineer an economic Revolution) was approved by our clinical research committee, the NHS West of Scotland Research Ethics Service (20-WS-0029 276667) and Health Research Authority (HRA). This study write up adheres to CONSORT guidelines.

Patients were eligible to participate if they were considered suitable by their Lincolnshire primary care team to take part; had GI symptoms meeting Rome IV criteria for the diagnosis of IBS-D; ≥ 18 years old; taking no prescribed treatment for GI symptoms. Patients were ineligible if they had previously been referred with IBS-like symptoms to a gastroenterologist or GI surgeon; had undergone investigations in secondary care for GI symptoms in the previous five years; had unexplained weight loss, rectal bleeding, fever, anaemia, palpable mass, previous history of inflammatory bowel disease, coeliac disease, pancreatic disease, cancer (except basal cell carcinoma), or abdominal surgery (except appendicectomy, hernia repair or diagnostic laparoscopy); were pregnant.

Study processes

Study nurses underwent structured training ending with formal assessment of the competencies required to manage alternative diagnoses.

Participants were given an information sheet and provided informed consent by physically signing the consent form or by electronic signature during virtual consultations when the screen was shared, or by email, text or verbally over the phone. The ethics committee approved these alternative forms of consent in addition to normal wet ink signature. Date of birth, biological sex, ethnicity, occupation, body mass index, comorbidities, medication and relevant family history were recorded. Participants completed five questionnaires at baseline and final follow-up either on paper, online or over the phone: IBS Symptom Severity Score (IBSSSS) which scores mild symptoms in the range of 75–174, moderate symptoms, 175–299 and severe symptoms, 300–500 [12]; Gastrointestinal Symptom Rating Scale (GSRS) modified to include the number of stools passed daily and their consistency for the last two weeks; Hospital Anxiety and Depression Score (validated for primary care, HADs) [13]; EQ-5D-5 L and SF12 quality of life scales [14]. Additionally, participants completed baseline economic questionnaires and monthly cost diaries. Participants randomised to the nurse arm completed a baseline questionnaire assessment of alcohol, caffeine and fibre intake and a GSRS questionnaire before every consultation.

Participants were given the choice whether Interviews were face to face, on-line or on the phone.

Participants were randomised 1:1 to either GP management (controls) or to a nurse-led, structured investigational approach and management guided by investigation results (intervention), using a purpose built, web-based data capture system (REDCap Cloud) using block randomisation with varying block sizes by the trials unit. The randomisation was stratified by IBSSSS (mild + moderate versus severe) and sex. Allocation concealment was maintained by storing the randomisation sequence securely within REDCap Cloud, where it could not be accessed by investigators, clinical staff, or personnel enrolling participants. Only the trials unit data manager, who had no role in recruitment or assessment, held administrative access to the randomisation module. Study staff triggered randomisation in REDCap after enrolment, at which point the allocation became visible.

Participants randomised to GP management, had a follow up appointment made with the GP. Participating practices were provided with a summary of recommended management (supplementary material (SM) 1). They were asked to follow this. However, GPs had clinical freedom to manage the patient as they felt appropriate.

The nurse-led managed arm underwent up to four protocolised management steps (described below and in SM3). If investigations at the first step were abnormal, participants were given an information sheet, specified treatment was provided and they were reassessed after 4–6 weeks. If the intervention had abolished abnormal symptoms, no further investigations were performed. Final follow up was arranged after at least three months and if still well, participants were discharged with their new diagnosis and treatment plan.

Participants only moved to the second and then on to subsequent steps if the previous step did not reveal a cause for symptoms or if troublesome symptoms persisted despite compliance with the intervention dictated by previous abnormal test findings.

The study aimed to minimise the investigations required for participants. Participants underwent tests only in the order specified, any treatments given were tried one at a time and no additional tests were requested if patients responded to standardised management provided after an abnormal test.

These steps were developed using principles advocated by the funder (NIHR). This included an initial 66 patient pilot study, detailed consultation with a patient and carer group who were asked to consider findings from this pilot and the nature and cost of investigations which could be arranged. Additional input into the trial design was provided by primary care leads in Lincolnshire.

The study was not designed to investigate the yield of all possible investigations that might be required to identify the cause(s) of diarrhoea.

The four possible steps in the nurse-led arm

Step 1: Initial assessments and tests

- Toileting habits.
- Dietary fibre/caffeine/alcohol intake (SM6-7).
- Assessment for lactose intolerance.
- Blood tests: full blood count, urea and electrolytes, coeliac serology, C-reactive protein, vitamin B12, folate, erythrocyte sedimentation rate, thyroid function tests, vitamin D.
- Pancreatic faecal elastase-1, faecal calprotectin, faecal immunological testing, stool microbiological culture.
- Glucose hydrogen methane breath testing (SM4).

Step 2

- ⁷⁵Selenium taurocholic acid (SeHCAT) scan.
- Fructose hydrogen methane breath test (SM4).

Step 3

- Upper GI endoscopy with small bowel aspiration (SM4) and duodenal biopsies and flexible sigmoidoscopy with random colonic biopsies.

Step 4

- low FODMAPs diet.
- The primary end point was change in IBSSSS at last follow up from baseline. Secondary end points included economic evaluation of healthcare and patient costs, change in quality of life, HAD scores, total GSRS scores (higher scores indicating greater impact of symptoms), individual symptom scores, time to symptom improvement and new GI conditions diagnosed.

Statistics, powering and analysis

A parallel design was used. The null hypothesis was that nurse management was not more efficacious than GP treatment.

It was assumed that 75% of participants would fall into the mild to moderate group and could be combined to assess as one group, and 25% into the severe group. A different effect size in the two groups was anticipated, so it was planned to test them separately, however, due to the smaller than expected sample size, final analysis was performed on data from both groups combined. A reduction in IBSSSS of 50 is the minimum clinically important

difference the study aimed to achieve [12], while accounting for 50% of the control group improving with NICE suggested treatments.

The expected value of the primary outcome in the control group was a mean IBSSS score of 125.4 in the mild to moderate group, and 372 in the severe group with a standard deviation of 53.4 and 66.0 respectively [12]. We assumed that 5% of the control participants would be treated similarly to the intervention group, leading to an inflation of the control group outcomes. We therefore aimed to detect a mean change of 47.5 between baseline and follow-up comparing the control and intervention group. Using a power of 85%, and alpha of 5% required 72 in the severe group and 48 in the mild to moderate group. After allowing for 10% loss to follow-up, the severe group rises to 80 and the mild to moderate group to 54. Resulting in a total number of participants needed of 134.

Participant characteristics and outcome scores at baseline were summarised descriptively by randomised allocation. The statistical analysis followed intention to treat principles. No interim analyses were planned or performed. The primary outcome was tested using a linear regression model adjusted for gender, IBS severity (mild/moderate and severe) and baseline IBSSSS using multiple imputations for missing outcomes. A standardised effect size (Hedges' *g*) was calculated for the primary outcome by dividing the adjusted between-group mean difference by the pooled post-intervention standard deviation and applying a small-sample correction factor. Multiple imputations used chained equations with the assumption of missingness at random, creating 10 imputed datasets and combining them according to Rubin's rules. Imputation models included baseline IBS severity, intervention, gender, and baseline IBS severity score as auxiliary variables. Secondary outcomes were assessed using the same regression model with multiple imputations. Logistic regression models, using only observed data assessed, whether the Nurse arm intervention decreased the likelihood of having moderate/severe GSRS symptoms at follow-up. No/minor (0) and moderate/severe [1] impact of symptoms on daily life for each symptom was used as the binary response variable, and adjusted by adding gender, IBS severity at baseline, baseline GSRS impact score as covariates. A linear regression model tested if the total number of visits with the nurses had an impact on the IBSSSS at follow-up.

For the predefined responder analysis (≥ 50 -point reduction in IBSSSS), between-group differences in proportions were assessed using Fisher's exact test (SM16), and absolute risk differences and numbers needed to treat (NNT) were calculated from observed risks.

To evaluate the plausibility of the missing-at-random (MAR) assumption, we compared baseline characteristics of participants who completed follow-up with those

who were lost to follow-up. There were no significant differences in baseline IBSSSS between completers and non-completers overall ($t(111)=0.49$, $p=0.628$), nor within either treatment arm (GP: $t(54)=0.003$, $p=0.998$; Nurse: $t(55)=0.897$, $p=0.374$). Attrition rates were also similar between the GP (32.1%) and Nurse (24.6%) arms (Fisher's exact $p=0.409$). These findings suggest that missingness was not systematically related to baseline severity or treatment allocation.

Sensitivity analyses examined the robustness to alternative missing-at-random and model specifications using: per-protocol and complete-case analyses; MI models with alternative covariates; mean substitution; and last-observation-carried-forward. All produced effect estimates consistent in magnitude and direction with the primary analysis. (supplementary material SM 10).

Analyses were conducted using Stata™ (version 18.0). Tests and reported p -values were two-sided with 95% confidence intervals, and significance levels set at $p<0.05$.

Economic analysis (SM2,5)

The economic analyses followed ITT principles and conducted using individual participant-level data using SAS 9.4 software. The economic evaluation followed published guidelines [15] and CHEERS statement recommendations [16].

Intervention costs were calculated using the cost which would occur when an intervention was delivered. Sensitivity analyses for a range of possible costs of the intervention were conducted. Follow up appointments and monthly patient diaries informed National Health System (NHS) services usage, out of pocket spending and sickness absence.

Prescribed medications were costed using British National Formulary prices [17]. Unit costs for health service use were derived from NHS reference costs [18], primary care costs from Personal Social Services Research Unit data [19]. Costs for individual stool or a bundle of typical blood tests were calculated using prices provided by the local NHS pathology laboratory. All calculated costs were adjusted for 2024.

The validated mapping function from the existing EQ-5D-3 L to the EQ-5D-5 L generated utility scores. The SF-12 scores were translated into SF-6D scores. Quality adjusted life years (QALYs) were calculated using the area under the curve. As the intervention period was 9 months, no discounting rates were applied.

Results (see also SM 9–17)

Between October 2020 and September 2023, 35 of 84 GP practices in Lincolnshire referred 257 patients, 134 (52%) met eligibility criteria. 113 (84%), of these 71.6% women, mean (SD) age 36.03 (13.26), were randomised (Fig. 1; Table 1 & consort statement in SM). The two arms were

well balanced. The IBSSSS characterised 62.8% as having severe symptoms. Mean (SD) follow-up was 11.0 (3.4) months for the GP arm and 11.5 (2.5) for the Nurse arm ($p=0.524$). The 28 participants who left the study had baseline characteristics not significantly different to those who completed the study (supplementary material).

Clinical outcomes

Primary end point

Mean (SD) IBSSSS changed from 303.00 (92.85) to 234.05 (114.20) in the GP arm and 312.00 (72.59) to 126.49 (85.26) in the Nurse arm. This lower IBSSSS at the follow-up assessment in the nurse arm was significant (adjusted difference (95% C.I.): -112.29 (-151.68 to -72.91); $p<0.0001$), corresponding to a large standardised effect size (Hedges' $g=0.95$). (SM10)

The proportion of participants achieving a ≥ 50 -point reduction in IBSSSS was 95.4% (41/43) in the nurse arm and 55.3% (21/38) in the GP arm, corresponding to an absolute risk difference of 40.1% and a number needed to treat of 3.

Secondary end points

At the start of the study there was no difference in the total GSRS or HAD scores (SM12-14). By the end of the study, participants in the Nurse arm had a significantly reduced total GSRS score compared to controls (adjusted difference (95% C.I.): -6.95 (-9.28 to -4.63); p -value <0.0001). Furthermore, moderate/severe GSRS scores for the majority of IBS relevant symptoms also reduced significantly more in the Nurse arm compared to the GP arm (Fig. 2).

There was a statistically significant improvement in quality-of-life scores in the nurse compared to GP arm participants using EQ-5D-5 L and SF12 ($p=0.019$ and <0.001) respectively. At the end of the study, there was no difference between arms for the HAD-D score (adjusted difference (95% C.I.): -1.21 (-2.73 to 0.31); p -value=0.115) however, nurse arm participants had significantly lower HAD-A scores (adjusted difference (95% C.I.): -1.75 (-3.46 to -0.04); p -value=0.044).

Intervention group

Of 57 participants randomised to nurse management, 43 completed the study (Table 2). All participants had the required blood tests, only one had an abnormality which led to a new diagnosis, a tissue transglutaminase level of 10u/ml. Duodenal biopsy and response to a gluten free diet confirmed coeliac disease.

Baseline stool samples were provided by 42 participants. Colonoscopy in two patients with abnormal FIT tests (14 and $>169\mu\text{g/g}$), identified no significant abnormalities. Faecal calprotectin levels were $<50\mu\text{g/g}$ in 32 patients, 50-171 $\mu\text{g/g}$ in nine and 209 $\mu\text{g/g}$ in one who

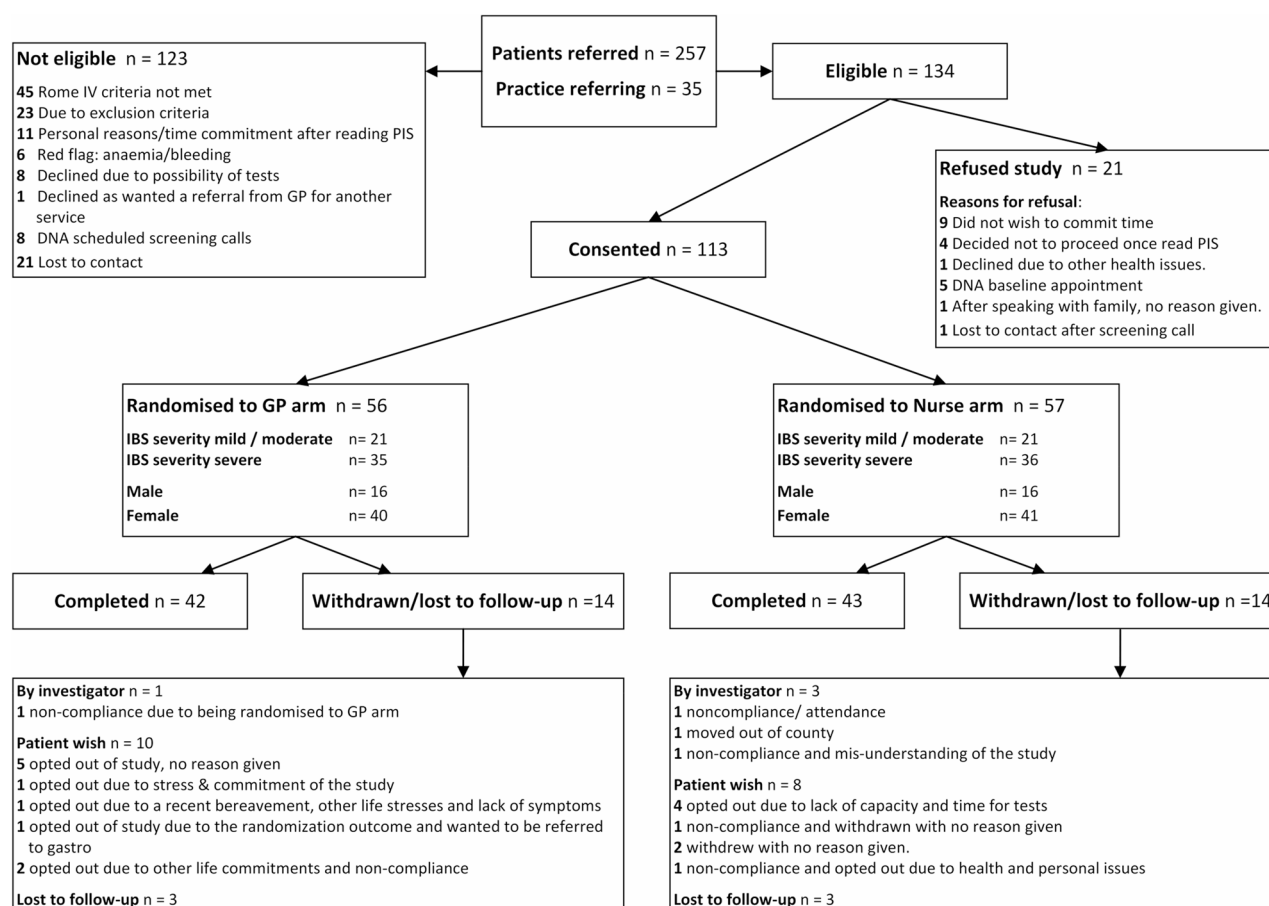


Fig. 1 A flow diagram indicating referral, recruitment, randomisation, follow up and patients withdrawn or lost to follow up in the Lincolnshire Poacher study

underwent colonoscopy which was normal. Thirteen participants with pancreatic faecal elastase levels $< 500\text{ug/g}$ were offered a trial of pancreatic enzyme replacement therapy (PERT).

Thirteen participants underwent 21 endoscopic procedures, 10 upper GI endoscopies, eight flexible sigmoidoscopies and three colonoscopies. Apart from one with coeliac disease all duodenal biopsies were normal. Small bowel aspiration identified possible small intestinal bacterial overgrowth (SIBO) in seven (organisms grown: Coliforms, *Pseudomonas Aeruginosa*, Streptococci, *Stenotrophomonas*, Enterococci). One participant was diagnosed with a hiatus hernia and grade A oesophagitis. All lower GI endoscopies and random biopsies were normal except for one where biopsies were reported to show: “non-specific focal areas of inflammation not compatible with inflammatory bowel disease”.

Response to treatment (see also SM18-23)

Results of investigations, compliance with suggested interventions and participant-reported sustained responses to treatment are shown in Table 2.

In seven participants, no new diagnoses were recorded as the outcome from interventions offered are unclear. In these, low FODMAPS diet (step 4) was discussed with one, but they did not try it.

Advice on lifestyle and toileting provided sustained benefit in 13 (30%) and 15 (35%) respectively. A diagnosis of bile acid diarrhoea was made in 18 (42%). A diagnosis of SIBO was made if a breath test was positive or if colonic bacteria and no contaminants were grown on a small bowel aspirate and the participant reported symptomatic response to antibiotics (either while taking the antibiotics or within 3–4 days of ceasing antibiotics and that response was sustained). In nine participants a response to first or second-line antibiotics was achieved, in four, SIBO was successfully treated after sensitivities were identified after small bowel aspiration. In 3 participants with abnormal aspirates consistent with SIBO, there was no obvious response to antibiotics and repeat aspirates were difficult to arrange because of either patient reluctance or constraints on endoscopy during the pandemic. Fructose intolerance was diagnosed in eight (19%). All participants with a faecal

Table 1 Patient characteristics

Baseline characteristics	Total (N=113)	GP Arm (N=56)	Nurse Arm (N=57)
Sex			
Female	81 (71.7%)	40 (71.4%)	41 (71.9%)
Male	32 (28.3%)	16 (28.6%)	16 (28.1%)
Age (years)			
Median (Q1–Q3)	33.42 (25.08–44.00)	34.13 (25.50–46.67)	33.42 (24.25–41.00)
Mean (SD)	36.03 (13.26)	37.48 (14.26)	34.60 (12.16)
Min–Max	18.67–80.58	19.33–80.58	18.67–68.33
Ethnicity			
White British	98 (86.7%)	47 (83.9%)	51 (89.5%)
White Other: including white non-British	12 (10.6%)	7 (12.5%)	5 (8.8%)
Other: including Mixed White and Middle Eastern	3 (2.7%)	2 (3.6%)	1 (1.8%)
Occupation ^a			
Managers/Directors/ Professionals/Technical occupations	54 (47.8%)	29 (51.8%)	25 (43.9%)
Administrative/Skilled trades/Caring/Leisure/ Service occupations	40 (35.4%)	24 (42.9%)	16 (28.1%)
Sales/Customer service/Machine operatives/Elementary occupations	25 (22.1%)	9 (16.1%)	16 (28.1%)
Retired/Unemployed/ Homemaker/Disability/ Unable to work/Student	39 (34.5%)	15 (26.8%)	24 (42.1%)
IBS SS score	307.54 (83.00)	303.00 (92.85)	312.00 (72.59)
Number of patients by IBS SS score severity			
Mild or moderate	42 (37.2%)	21 (37.5%)	21 (36.8%)
Severe	71 (62.8%)	35 (62.5%)	36 (63.2%)
IBS SS score by severity			
Mild or moderate	217.64 (52.22)	201.90 (58.74)	233.38 (40.26)
Severe	360.72 (41.32)	363.66 (42.62)	357.86 (40.41)
Total GSRS score	18.39 (5.87)	18.66 (5.82)	18.12 (5.95)
HAD-D score	4.60 (3.29)	4.30 (3.21)	4.89 (3.38)
HAD-A score	8.78 (4.30)	8.63 (4.11)	8.93 (4.51)

Data are either frequency (%) or mean (standard deviation) if not indicated otherwise

^a Participants could fall within more than one category

elastase <500ug/g were offered a trial of PERT, not just those with levels suggestive of moderate/severe PEI. Of these 3 (27%) all with a faecal elastase level in the 200–500ug/g range had a sustained response. exocrine pancreatic insufficiency ($n=3$, 7%). Lactose intolerance was diagnosed in two participants (5%) and coeliac disease (in one (2%). More than one condition was diagnosed in 12 participants (28%).

Discharge from follow up after a satisfactory sustained improvement in symptoms occurred after two to seven consultations, with more than half the participants discharged within four consultations (SM21–22). Total number of visits did not impact on the follow-up IBSSSS (−8.29 [−21.35 to 4.76], $p=0.206$). There were no serious adverse events related to trial interventions.

Control group

Of 42 participants who completed the study randomised to GP care, 24 (57%) had investigations requested by their primary care team which are not recommended in the NICE guidelines. 19 had extensive blood tests, 17 had stool tests which included one or more of the following: microbiological stool culture, calprotectin, H. Pylori testing, FIT testing or faecal elastase. Five were referred for secondary care gastroenterological or colorectal surgical opinions which resulted in eight radiology tests (three abdominal ultrasounds, two small bowel MRI scans, one SeHCAT scan and one CT scan of abdomen and pelvis) and four endoscopic procedures, one OGD, one flexible sigmoidoscopy and two colonoscopies. No significant abnormalities were identified by any of these investigations.

Healthcare costs

The mean total cost was £1395.80 for nurse and £314.70 for GP arm participants. The increased nurse arm costs were due to participants being seen more frequently (total 196 nurse v 99 GP arm appointments), cost of diagnostic tests (supplementary material Tables 4, 11–13, 15, 16 and Figs. 5, 6, 7 and 8) and the training cost for the nurses (total 222 h (111 h /nurse), cost £14,645, a mean training cost of £256.90/ patient. Incremental cost-effectiveness ratios (ICERS) and cost per quality adjusted life years (QALY) are shown in Table 3. (See also SM23–30)

Discussion

This randomised controlled trial suggests that a significant clinical benefit occurred in both control and intervention groups however, stepwise investigation and targeted treatment of alternative diagnoses in the intervention group produced greater benefit.

Despite the highly statistically significant findings, there are reasons to be cautious about our results. First, this study was potentially underpowered because of under-recruitment and higher-than-expected loss to follow-up. Both these factors were exacerbated by the COVID-19 pandemic. Our power calculation was based on one third of participants presenting with severe and two thirds with mild symptoms. Instead, these proportions were reversed. Data suggests that larger effects would be seen in more severely affected patients [12], which we did observe in this study, so it is possible that

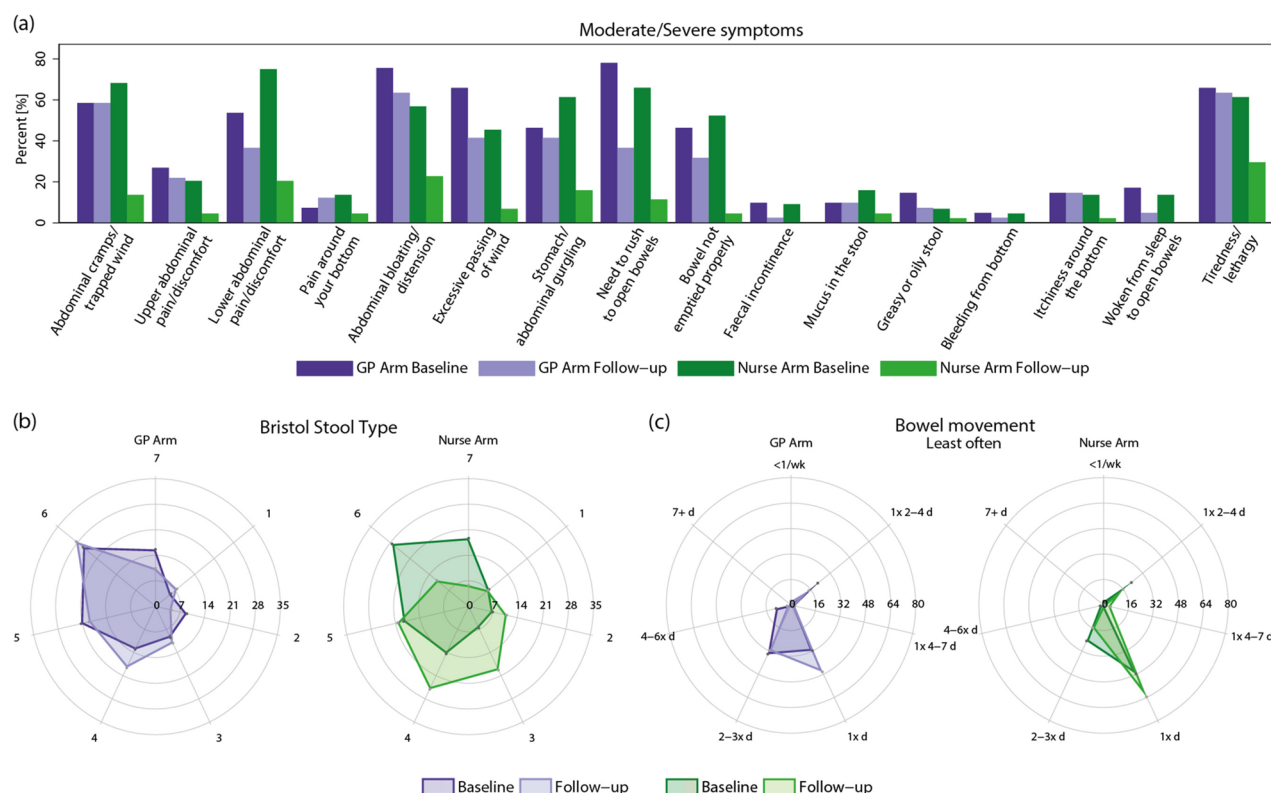


Fig. 2 **a** Change in % of participants reporting moderate or severe GRS symptoms relevant to IBS (see supplementary data for all symptoms, and statistical model results), **(b)** changes in stool consistency, and **(c)** frequency of bowel opening for both arms at baseline and follow-up

our original power calculation indicated a higher-than-needed rate of recruitment. Retrospective power calculations are not appropriate, so, while our primary outcome was statistically significant and the observed effect size was robust, additional studies are required to exclude the possibility that the effects detected may not be real or that smaller, relevant, effects may not have been detected.

A further limitation relates to missing outcome data. Loss to follow-up was higher than anticipated, however, baseline IBSSSS and withdrawal rates did not differ significantly between completers and non-completers or between study arms. This supports the assumption that data were missing at random. Sensitivity analyses, including complete-case models, per-protocol analyses, alternative multiple-imputation models and simple substitution methods, produced effect estimates that were consistent with those from the primary analysis. These findings indicate that our results were robust to different assumptions about missing data.

Thirdly, the study population may not be representative of the UK population in view of high proportion of participants with severe symptoms and the unusually high trial enrolment rate. A simple likely explanation is that severe symptoms are difficult to tolerate, that working from home allowed many people with milder symptoms to manage better, and during the pandemic they hesitated

to contact ‘overburdened’ primary care services. On the other hand, recruitment of twice as many women as men is consistent with the population prevalence.

Additionally, GPs arm participants may not have been provided with the same support as the nurse group and we did not undertake to collect details of individual management by GPs. The study design was intentionally ‘real world’ for control arm GPs who although accepting written information outlining the NICE guidelines and being encouraged to adhere to NICE guidelines, retained clinical discretion to deviate from the guidelines. Indeed, more than half the GPs performed investigations which are not recommended by NICE and 12% of control participants were referred to secondary care. It is notable that no treatable cause for symptoms was detected from those referrals. While GPs may not adhere to current NICE guidance, clinically important improvements were seen in the GP arm.

The quality of the interaction between health care provider and patient can influence outcomes. This study was unblinded, and the primary outcome was patient-reported. The nurse-led arm involved more frequent contact and possibly, clinical assessment was more structured. There is a possibility that the knowledgeable, specialist nurses empathised with the participants better than those randomised to care by their busy GP.

Table 2 Investigations in the nurse arm participants who completed the study ($n=43$) which led to a potential therapeutic intervention and the numbers reporting definite benefit from each intervention. Recorded compliance with the intervention is according to what participants reported

Tests performed	Total number of participants who were assessed	Numbers and % of the nurse arm cohort identified with potentially abnormal result and intervention was suggested	Numbers who complied with suggested treatment (%)	Numbers and % of those with the abnormal test result reporting benefit from the intervention
Lifestyle assessment				
Fibre intake	43	13 (30%)	12 (92%)	6 (50%)
Excess Caffeine	43	13 (30%)	11 (85%)	5 (46%)
Excess Alcohol	43	7 (16%)	7 (100%)	3 (43%)
Lactose Intolerance	43	6 (14%)	3 (50%)	2 (67%)
PFE	43	40 (93%)	36 (90%)	5 (14%)
Positioning	43	24 (56%)	17 (71%)	13 (77%)
Blood tests				
Coeliac screen	43	1 (2%)	1 (100%)	1 (100%)
Low Vitamin B12	43	2*	2* (100%)	1 (50%)
Low Vitamin D	43	39 (91%) **	27 (69%)	6 (22%)
Stool tests				
Faecal elastase	42	13 (31%)	11 (85%)	3*** (27%)
FIT test	42	2 (5%)	2 (100%)	n/a
Culture	42	0	-	-
Breath test				
Glucose	42	18 (43%)	n/a	8 (44%)
Fructose	25	19 (76%)	9 (47%)	8 (19%)
SeHCAT scan	34****			
Severe BAD		4 (12%)	3 (75%)	3 (100%)
Moderate BAD		9 (27%)	9(100%)	9(100%)
Mild BAD		2 (6%)	2 (100%)	2 (100%)
Borderline BAD		3 (9%)	3 (100%)	1 (33%)
No SeHCAT scan	1 *****	1	1 (100%)	1 (100%)
Normal scan	16			
Endoscopy				
Upper GI	10	9 (90%)	9 (100%)	9 (100%)
Duodenal biopsy	10	1 (10%)	1 (100%)	1 (100%)
Duodenal aspirate	10	7 (70%)	7 (100%)	4 (57%)
Flexible sigmoidoscopy	8	0	-	-
Colonoscopy	3	0	-	-
Random colonic biopsy	11	0		

PFE Pelvic floor exercises

* 2 nurse arm participants with borderline Vitamin B12 levels started by their GPs on Vitamin B12 replacement. The trial protocol indicated that for borderline levels, the trial team would repeat them and if required would inform the primary care team about replacement if required but GP action pre-empted this approach

**Borderline 25 hydroxyvitamin D levels between 50–70 nmol/l were seen in 19 and low/ very low levels of 14–50 nmol/l identified in 18 participants

*** Both participants with an unequivocal clinical response to PERT had a faecal elastase result in the range 200–500ug/g. Only one participant in this study has a FE-1 level of < 200ug/g, they did not respond to PERT and subsequently were found to have SIBO with and excellent sustained response to antibiotics

**** Of participants with an abnormal SeHCAT scan result, 10 patients required a change to their initial treatment for BAD, either to a sequestrant when a low-fat diet was initially suggested or change from Colestyramine to Colesevelam

*****This participant declined to have a SeHCAT scan as they worked with children and was not reassured that there was no risk from the radiation dose. Their symptoms of dietary fat intolerance were convincing, they were empirically trialled with a bile acid sequestrant to excellent clinical effect

The CONSORT extension for pragmatic trials aims to improve the reporting of trials like ours. We have followed this standard but nevertheless our observed adjusted mean difference (–112 points) is large. While our approach was novel and could account for this large difference, we acknowledge that the structure of this study carries risk of placebo response and bias. To

explore this possibility, we investigated the relationship between the number of appointments and degree of improvement but found no correlation. Additionally, we followed participants up for at least three months after they reported symptom improvement and observed that their symptoms remained stable throughout this period. However, three months follow up is a short period and

Table 3 Costs, QALYs and Incremental cost-effectiveness ratios (ICERS) based on imputed EQ5D and SF12 data adjusted by the baseline score for the nurse compared to GP arm (these data with personal and societal costs included - see supplementary data)

	Cost (£) mean (95% CI)	Incremental Cost (£) mean (95% CI)	QALYs mean (95% CI)	Incremental QALY mean (95% CI)	ICER (£/QALY) mean (95% CI)
EQ5D-5L					
GP arm	316 (249, 393)		0.758 (0.743, 0.774)		
Nurse arm	1398 (1260, 1537)	1082 (918, 1237)	0.783 (0.763, 0.802)	0.025 (0, 0.049)	41706 (15649, 219452)
SF-12					
GP arm	316 (249, 393)		0.608 (0.598, 0.617)	314 (249, 396)	
Nurse arm	1398 (1260, 1537)	1082 (918, 1237)	0.643 (0.634, 0.651)	0.035 (0.022, 0.048)	31070 (21290, 49661)

it is well documented that trials of intervention for many gastrointestinal disorders frequently have high placebo response rates [20]. Furthermore, results can be biased as a result of participants changing their lifestyle or behaviour simply because they are participating in a study (the 'Hawthorne effect'). It is also possible that the process of arranging tests in itself may lead to improvement.

NICE guidelines advocate as a first step, assessment of lifestyle factors. The lifestyle areas addressed in the intervention arm, were identified by our patient advisory group as important during the study design. They advised that we should tackle issues which should be part of a holistic conversation but are frequently neglected. Our nurses used questionnaires to help objective assessment of lifestyle issues. Whilst most patient with IBS-like symptoms have modified their diets to little avail, evidence linking dietary factors to the cause of IBS-like symptoms, is weak [21]. Therefore, we focused on those dietary factors which could be easily quantified or had better evidence to support their importance: caffeine, alcohol, fibre and lactose. When required (frequently), intervention arm participants were taught how to sit on the lavatory to facilitate defaecation and discussed the benefit of pelvic floor exercises which can help patients with diarrhoea, especially when complicated by bloating, urgency or incontinence [22]. We did not measure the absolute benefit of the individual lifestyle interventions but in 12% participants reported that this led to adequate improvement (SM 23) and no further intervention was required.

While NICE guidelines for primary care suggest that few investigations are needed in these patients, this approach is not shared by British Society of Gastroenterology (BSG) guidelines for managing chronic diarrhoea [23] or IBS [24].

All British guidelines agree that screening for coeliac disease is worthwhile. In this small study, we did not find that other blood tests apart from vitamin B12 and vitamin D levels changed management. The yield from blood testing is generally agreed to be low.

NICE state that stool testing is not required. However, a variety of stool tests including culture, helicobacter antigen, calprotectin and FIT testing, were requested, sometimes several times, in a large majority of the control arm patients. Calprotectin is recommended in secondary care guidelines but given the much lower incidence of inflammatory bowel disease (IBD) compared with IBS in primary care, one would not necessarily expect to find new IBD frequently. While no UK guidelines for IBS recommend routine stool testing for occult blood, in our pilot study, in a low-risk group of patients we found two early cancers. Given the increasing numbers of young patients diagnosed with bowel cancer, at the request of the patient advisory group, we routinely arranged FIT testing in the intervention arm. It did not change management, although abnormal FIT tests generated 3 colonoscopies.

Testing for faecal elastase is not recommended by any UK IBS guidelines. However, studies including 3,304 patients have reported moderate or severe pancreatic exocrine insufficiency (PEI) mimicking IBS in 2.3–13.3% [25–28]. We identified PEI as a possible issue in our pilot study and in this trial, PERT improved the outcome of 7% participants in our study. All had FE levels between 200–500ug/g and no risk factors for PEI. UK PEI guidelines [29] do not discuss management of a FE level between 200–500ug/g. One retrospective study suggests that there is a reasonable response rate in this patient group to PERT [30]. FE levels <500ug/g may be seen if the stool sample is diluted by liquid, in the presence of SIBO, untreated coeliac disease or PEI. One quarter of our participants had a FE level <500ug/g, and one quarter of those responded to PERT. Another quarter were later diagnosed with SIBO. Participants were carefully instructed to supply formed stool samples and our laboratory usually rejects stool samples considered unsuitable sent for faecal elastase analysis so the cause for low FE levels in the others is unclear. The risks from a therapeutic trial of PERT are extremely low. Our data are far from definitive. Further studies are required whether this patient group should be investigated with faecal

elastase and the response rates in people with a FE level of 200–500ug/g.

The diagnosis and frequency of small intestinal bacterial overgrowth is another extremely contentious area within gastroenterology. It is not recommended in either NICE or BSG guidelines for IBS but empirical therapy without any testing is recommended if SIBO is suspected in BSG guidelines for diarrhoea. There are substantial data which suggest that patients with IBS appear to have an increased prevalence of SIBO and that antibiotic treatment of SIBO seems to bring demonstrable clinical benefit; patients with IBS have higher response rates to antibiotics than other groups with SIBO [31]. However, some authorities remain very critical of the accuracy of breath testing in patient with IBS-like symptoms [32].

The sensitivity and specificity of glucose hydrogen methane breath testing which we used in this study is generally considered better than lactulose breath testing. The addition of duodenal aspiration when there was a positive breath test but no response to standard antibiotics, identified that bacterial resistance to standard antibiotics or unexpected organisms occur relatively frequently and this may be part of the problem in published studies which have used only one line of antibiotics. While small bowel aspiration is rarely performed in routine practice, aspiration to provide a qualitative rather than a quantitative assessment for SIBO is straightforward and quick to do during upper GI endoscopy [33]. Other groups have also suggested that small bowel aspiration has a useful second line role to identify patients with SIBO [34, 35]. However, it is also well described that a response after antibiotic therapy may occur for reasons other than an antibiotic effect on colonic bacteria colonising the small bowel.

Our patient advisory group felt that antibiotic stewardship mandated that we use testing, however imperfect, to help with clinical decision making. In this study, we recorded a diagnosis of SIBO in participants only after an abnormal breath test or an aspirate which grew colonic bacteria and a sustained symptomatic response to antibiotics and in some patients, especially those with dual pathology, we also checked that the breath test normalised after antibiotic therapy. While guidelines suggest that tests for SIBO should not be performed because the tests are suboptimal, the use of empirical antibiotics without testing is also problematic. The literature suggests and our data supports this, that in this very large patient group, there do seem to be some who achieve sustained symptomatic response after antibiotics, further research to identify who they are and which antibiotic they should receive is urgent.

BAD was the most common diagnosis made. Treating BAD led to sustained benefit. Investigating for BAD is not advocated by NICE. However, it is recommended

in secondary care guidelines. Delays in diagnosing BAD are often prolonged, are costly and affect mental health [36]. Open access for primary care to diagnostic SeHCAT scans would reduce such delays [37].

Endoscopic assessment was performed in one quarter of participants, it confirmed oesophagitis, coeliac disease or treatable SIBO in one third. Lower GI endoscopy did not identify any treatable disorders. Our findings are consistent with published data that the yield of endoscopy is low in this patient group [8]. Systematic review suggest that microscopic colitis affects 3% of the population with diarrhoea attributed to IBS (these are all secondary care studies so the frequency in primary care is likely to be much lower), FIT negative cancers do occur in this population, proctitis without elevation of calprotectin is described and duodenal biopsies do identify villous atrophy in approximately 2% people who have normal coeliac serology [10]. Endoscopic assessment, the last diagnostic step in our management approach, was not required by most participants because their symptoms had improved adequately. On a practical level this is helpful, because it is difficult to imagine how UK endoscopy services could cope with a large influx of new patients.

In this study, we identified 7% of patients with fructose intolerance. This diagnosis is rarely considered in the UK; if present, it responds well to dietary change but would also respond to a low FODMAPs diet. We did not assess for other mono and di-saccharide intolerances which could possibly cause similar symptoms [38].

We attempted to assess economic parameters. Our costs estimates, because of the small sample size, have wide confidence intervals. Importantly, we were not able to capture the costs associated with incorrect diagnoses. Accurate diagnosis allows correct treatment whereas misdiagnosis leads to ineffective prescribing and ongoing medical and social costs of the revolving door of patients repeatedly seeking solutions for persisting symptoms. Of note, almost one fifth of the nurse arm costs was their training. In a real-world clinical setting, these nurses would see far more patients than in this trial making the training costs substantially smaller.

The hypothesis tested in this study that symptoms caused by functional conditions can be mistaken for IBS is supported by evidence but expert opinion varies which investigations are appropriate. It is surprising that almost no previous studies have been performed either in primary or secondary care to identify which investigations sufferers should undergo. In our participants, diagnoses other than IBS were identified with a frequency consistent with previously published data [10]. It is also confusing that NICE guidance differs so substantially from BSG guidelines. Our study suggests that structured, nurse-led assessment including targeted investigation is achievable for a relatively modest cost in primary care. There is

a need for urgent additional research with larger sample sizes and particularly more detailed assessment of the importance of PEI and SIBO to confirm and extend or to refute our findings.

Abbreviations

BAD	Bile acid diarrhoea
BSG	British Society of Gastroenterology
CI	Confidence intervals
CRF	Clinical Research Form
FCP	Faecal calprotectin
FE	Faecal elastase
FIT	Faecal Immunochemical Test
FODMAPs	Fermentable, Oligo-saccharides, Di-saccharides, Mono-saccharides and Polyols
GI	Gastrointestinal
GP	General practitioner
GSRS	Gastrointestinal Symptom Rating Scale
HAD	Hospital Anxiety and Depression scale
IBSSSS	Irritable bowel syndrome symptom severity scale
ICER	Incremental cost-effectiveness ratios
NICE	National Institute of Health Care Excellence
NIHR	National Institute for Health and Care Research
PEI	Pancreatic Exocrine Insufficiency
PERT	Pancreatic Enzyme Replacement Therapy
PFE	Pelvic floor exercises
QALYs	Quality-adjusted life year
SD	Standard deviation
SeHCAT	⁷⁵ Selenium taurocholic acid scan
SIBO	Small Intestinal Bacterial Overgrowth
SM	Supplementary material

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12875-026-03293-7>.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

HJNA Chief investigator, study guarantor of the study, developed the study protocol, obtained the funding, trained the nurses, supervised the study, contributed to the analysis, drafted all the manuscript versions. DJ Research manager: obtained the funding, developed the study protocol, supervised the nursing team, coordinated the participating practices, supervised data collection and uploading onto the trial database, contributed to the analysis, contributed to all drafts of the manuscripts, and approved the final draft. KR Research nurse: Helped run the study, delivered the intervention, collected participant data, contributed to the analysis, contributed to all drafts of the manuscript, and approved the final draft. AJ Research nurse Helped run the study, delivered the intervention, collected participant data, contributed to the analysis, contributed to all drafts of the manuscript, and approved the final draft. AC Senior nurse researcher developed the study protocol, helped train and supervise the nursing team, contributed to all drafts of the manuscript, and approved the final draft. ANS Professor of primary care developed the study protocol, helped obtain the funding, helped supervise the intervention, assisted with the analysis, contributed to all drafts of the

manuscript, and approved the final draft. SR Professor of Nursing developed the study protocol, helped obtain the funding, trained the nurses, helped supervise the intervention, contributed to all drafts of the manuscript, and approved the final draft. KW Research nurse coordinated all regulatory matters, supervised the randomisation, coordinated the participating practices, attended the weekly MDT meeting during the study contributed to all drafts of the manuscript, and approved the final draft. JC developed the study, helped obtain the funding, ran the clinical trials unit, guarantor of the data integrity, helped supervise the trial, contributed to all drafts of the manuscripts, and approved the final draft. VP Patient representative from the trial development group who then joined the trial steering committee, helped develop the protocol and then the patient information sheets, monitored trial progress, contributed to all drafts of the manuscript and approved the final draft. RB Patient representative from the trial development group who then joined the trial steering committee, was co-applicant on the funding application, helped develop the protocol and then the patient information sheets, monitored and supported trial progress, contributed to all drafts of the manuscript, and approved the final draft. BW Patient representative from the trial development group who then joined the trial steering committee, helped develop the protocol and then the patient information sheets, monitored trial progress, contributed to all drafts of the manuscript and approved the final draft. MS Health economist, developed the study, helped obtain the funding, devised and supervised economic data collection, contributed to all drafts of the manuscript and approved the final draft. SH Local GP and medical director of the ICB, developed the study, helped obtain the funding, helped with GP practice recruitment, attended the trial steering committee, contributed to all drafts of the manuscript and approved the final draft. SZ Health economist performed all the economic analysis after MS left Lincoln, contributed to all drafts of the manuscript and approved the final draft. He is guarantor of the economic data. TKK Statistician cleaned the data, helped perform the first statistical analysis, drafted all the tables, performed additional analyses, contributed to all drafts of the manuscript and approved the final draft. ZA Chief statistician, took over after GL retired, guarantor of the final statistical analyses, contributed to all drafts of the manuscript and approved the final draft. GL Professor of statistics, developed the study, helped obtain the funding, supervised the study, wrote the statistical analysis plan. Reviewed manuscript, and approved the final draft.

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Data availability

All the trial data is recorded by Hull Health Trials Unit in an independently held, secure database. The database was locked on completion of the trial, after data checking and cleaning and before analysis. The Hull trial unit has undertaken to create an anonymised dataset and make it discoverable with a streamlined data access request process, on publication of the study.

The following will be made available:

- All recorded trial data including anonymised CRFs
- Individual identified participant data (including data dictionaries)
- Additional documents which include the study protocol, information sheets, questionnaires used, anonymised clinical letters and reports and the statistical analysis plan

Once the study is accepted for publication we will ask the Trials Unit prepare the dataset and it will remain available for appropriate research use (as defined by standard protocols used by the Trials Unit) for at least 15 years, including any further analyses deemed of relevance. It is anticipated that it will become available within one to two months of the publication date.

Declarations

Ethics approval and consent to participate

The Lincolnshire Poacher study was approved the NHS West of Scotland Research Ethics Service (20-WS-0029 276667) as stated in the manuscript p4. This study adhered to the Declaration of Helsinki. Participants were given an information sheet and provided informed consent by physically signing the consent form or by electronic signature during virtual consultations when the screen was shared, or by email, text or verbally over the phone. The ethics

committee approved these alternative forms of consent in addition to normal wet ink signature as the trial was undertaken during the pandemic.

Competing interests

Free SeHCAT capsules for this study were provided by GE HealthCare Pharmaceutical Diagnostics, Amersham. No author had any other conflict of interest.

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