The Lincolnshire Poacher Study Protocol V2.3 09.03.2021

Organic disease masquerading as IBS: an RCT in primary care: The Lincolnshire Poacher Study (Promoting Optimal Assessment to Change Health and Engineer an Economic Revolution)

Short Title: The Poacher Study

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Contents

Section:

1. Summary:

Background: Irritable Bowel Syndrome (IBS), a chronic relapsing disorder, is diagnosed by symptom-based criteria in the absence of detectable organic causes. IBS frequently leads to severely impaired health related quality of life. IBS-like symptoms, affecting up to 20% of the population, carry significant costs for sufferers, society and healthcare.

The National Institute for Health and Care Excellence (NICE) directs that a limited number of tests are performed when someone presents with IBS-like symptoms. If these tests are normal, lifestyle modifications or specified medication should be prescribed. However, >50% of patients diagnosed with IBS do not improve with this approach.

This may be because alternative conditions are missed particularly when people have IBS-like symptoms characterised by diarrhoea. Evidence suggests that >75% of these patients have other diagnoses, particularly pancreatic insufficiency, microscopic colitis, small bowel intestinal overgrowth carbohydrate malabsorption or bile acid diarrhoea.

Clinical history taking is inaccurate at identifying the cause for symptoms, whereas targeted investigations diagnose these conditions precisely.

In patients with IBS-like symptoms characterised by diarrhoea, no studies have examined the cost-effectiveness and health benefits of early, more comprehensive investigations.

Data show that nurses using checklists, can assess patients accurately, arrange appropriate investigations and apply treatments effectively achieving improvement in symptoms comparable to gastroenterologists even when patients have complex underlying gastrointestinal disorders.

Methodology: This study will assess whether patients with IBS-like symptoms fulfilling Rome IV criteria for diagnosis of mixed constipation/diarrhoea or diarrhoea predominant IBS, presenting to primary care benefit from nurse-delivered care, which includes investigations and management denied by NICE, compared with standard care delivered by a GP following NICE recommendations.

Additionally, an economic analysis will be undertaken examining the costs for patients and healthcare in each arm of the study and a qualitative process evaluation, including semi-structured interviews with the nurses, GPs and a selection of patients, to understand the contextual factors which will facilitate wider application of our approach.

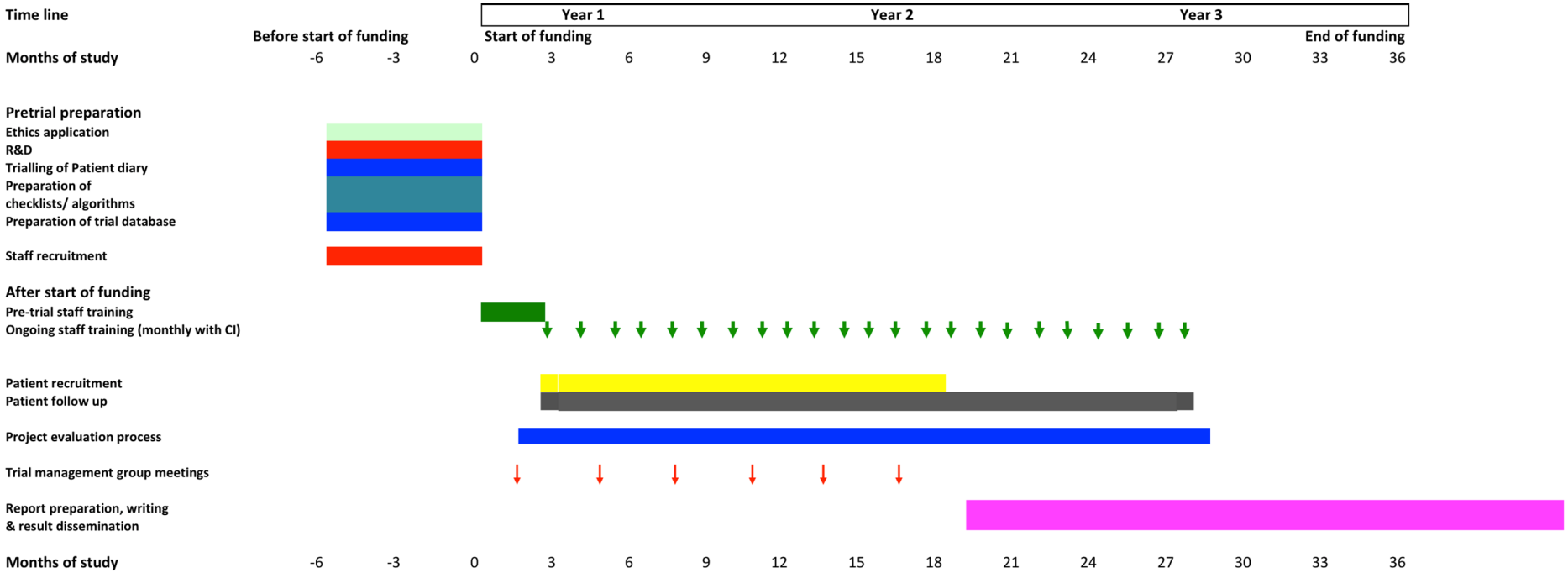
Research plan:, After providing informed consent to participate, eligible patients will be stratified by IBS severity and gender, then randomised to care by a GP following NICE guidance or to a research nurse, specially trained to use structured investigations to identify organic pathology and equipped with treatment protocols targeting abnormal investigation results.

Recruitment of 134 patients will give the study 85% power to detect clinically significant improvement in the primary endpoint, IBS severity scoring system (IBSSSS) score at one year allowing for 10% patients loss to follow up and 5% GP deviation from NICE guidance.

2. Schedule of events

Procedure	Pre-study assessments	Initial clinic appointment	Initial investigations	Follow up: Initiate treatment or 2nd/3rd/4th /5th line investigations (nurses arm only)	Follow up	End of study
Primary Care team referral to the study for IBS-like symptoms	Ö					
Patient contacted, inclusion/ exclusion criteria checked, study explained	Ö					
If interested, information sheet given to patient and contacted 1 week later to confirm on-going interest	Ö					
Consent procedure (including e-consent)	Ö					
Patient symptom self-assessment questionnaire GSRS	Ö			Ö (in nurse led clinic)	Ö (in nurse led clinic)	Ö
Other questionnaires **IBS Severity Score (IBS SSS)** **PHQ-12 SS score** **SF12** **EQ-5D-3L** **HAD**	Ö					Ö
Randomisation	Ö					
Clinical assessment in primary care / or by virtual consultation by Primary care team		Ö		Ö	Ö	
Economic evaluation		Ö	Ö	Ö	Ö	Ö
Qualitative process evaluation					Ö	

3. GANNT Chart showing the time lines for the Lincolnshire Poacher Study



4. Background

This randomised trial aims to assess whether specially trained nurses can improve outcomes for patients presenting for the first time with IBS-like symptoms compared to standard care delivered by a GP. In this study, GPs will follow NICE management guidance for patients with a diagnosis of IBS. The nurses will be trained to follow detailed checklists and a management algorithm which will include additional, mostly non-invasive, well tested investigations which are not included in NICE recommendations but have the ability to identify organic diagnoses which mimic IBS and which would otherwise be missed. The cost of both approaches for patients and healthcare will be measured and trial participants will be followed for one year to assess whether any symptom improvements are maintained.

IBS is defined by symptom-based diagnostic criteria in the absence of detectable organic causes. It is a chronic, often lifelong relapsing disorder in which abdominal pain and /or discomfort is associated with a change in bowel habit or defaecation. The definition of relevant symptoms have been refined over many years at expert consensus meetings. Recently updated criteria termed the "Rome IV" criteria were published in 2016.

Many large studies from primary and secondary care and encompassing different cultures around the world have consistently documented that in the population seeking healthcare, those diagnosed with IBS-like symptoms, a prevalent and expensive condition have a surprisingly poor health related quality of life (HRQoL). Indeed, the HRQoL across most domains is comparable to conditions which carry a high mortality, such as ischaemic heart disease, heart failure and diabetes mellitus.

It is more common in women than men, in lower socio-economic groups and mostly diagnosed in younger patients. Patients with IBS visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalised more frequently, and consume more overall direct costs than those without IBS. Resource utilization is highest in patients with severe symptoms and poor HRQoL. Many community-based studies indicate that IBS with diarrhoea predominance or with mixed IBS diarrhoea/constipation are more prevalent than IBS with predominant constipation.

When IBS is associated with intermittent or constant diarrhoea, quality of life is generally lower than when IBS is predominantly associated with constipation. Women with IBS have a lower level of quality of life than men and consistently report higher levels of intestinal and non-intestinal symptoms despite similar levels of IBS severity, abdominal pain, psychological symptoms and illness impact. Distress is highest among younger patients with IBS.

As a result of IBS symptoms, US and UK data suggest that the mean number of days (8.5 - 21.6) lost to work per year[1] is significantly more than for people without IBS and when at work, IBS sufferers have lower productivity. This has economic consequences for both the sufferer and their employer. However, the true costs of this disease for patients and society are poorly characterised.

In the UK, IBS affects up to 20% of the population at any one time although many patients with IBS do not seek medical advice. However, once an individual is diagnosed with IBS, they utilize healthcare services more than people without IBS. It has been estimated that a full time GP sees on average eight patients with IBS a week (one of whom is presenting for the first time)[2] costing the NHS £22 million/year for consultations[3] and more than £70 million

for prescriptions issued afterwards[4]. Whilst the National Institute for Health and Care Excellence (NICE) advises that these patients with typical symptoms of IBS do not require referral to secondary care, nevertheless patients with IBS account for approximately 7.5% of total out-patient attendances in British secondary and tertiary care gastroenterology and colorectal surgical clinics, at a cost of at least £12 million in 2012–2013.[4].

Using the Rome IV criteria as the benchmark for the diagnosis of IBS, in 2017, NICE updated their recommendations that in patients presenting to primary care with typical IBS-like symptoms the following tests should be undertaken to exclude other diagnoses: full blood count, erythrocyte sedimentation rate, C-reactive protein and antibody testing for Coeliac disease.

NICE categorically stated that a number of tests are unnecessary to confirm diagnosis in people who meet the IBS symptom diagnostic criteria including ultrasound, sigmoidoscopy, colonoscopy, barium enema, thyroid function tests and any faecal testing or breath testing.

For patients meeting their criteria for a diagnosis of IBS, NICE acknowledges that while no treatments for diarrhoea predominant IBS are effective in even a majority of patients, some patients respond to a wide variety of treatments: changes in carbohydrate intake, gluten avoidance, wheat free diets, antibiotics, probiotics, antidepressants, opioid receptor agonists/antagonists and some complementary therapies. If these failed to improve symptoms, NICE recommended that consideration should be given to the use of one or more of the following drugs: antispasmodics, laxatives, loperamide, tricyclic or selective seretonin reuptake inhibitor antidepressants [5-12].

However, NICE acknowledge that at least 50% of patients will continue to have unresolved symptoms long term[13, 14] despite following their recommended approach.

The simple conclusion is that patients with IBS-like symptoms are not suffering from a single condition and indeed, the key criticism of the symptom-based approach for the diagnosis of IBS is that symptoms are an unreliable way to distinguish patients with organic treatable pathology from those with true IBS[15].

This is particularly true when patients with IBS-like symptoms have intermittent or persistent diarrhoea. Data from many studies suggest that treatable organic pathologies can be detected in the majority of this patient group[15] if they are investigated more intensively than NICE recommends. The potentially missed diagnoses and the frequency with which they occur in patients meeting the criteria specified by NICE for the diagnosis of IBS are as follows:

1.	Infectious diarrhoea	<1%
2.	Inflammatory bowel disease	<1%
3.	Cancer	<1%
4.	Non-coeliac gluten sensitivity[8]	c5%
5.	Pancreatic insufficiency[5]	7%
6.	Microscopic colitis[6]	10%
7.	Small bowel intestinal overgrowth[7]	40%
8.	Carbohydrate malabsorption[8]	35-64%
9.	Bile acid diarrhoea [9, 10].	25-33%

The best evidence showing that organic diagnoses are frequently missed in this patient group come from patients with a condition called bile acid diarrhoea, which is the cause for

symptoms in 25-33% of patients confidently diagnosed with IBS[9, 10]. Data suggest that almost half of patients diagnosed with bile acid diarrhoea wait for more than 5 years to be diagnosed and many patients report that their symptoms are repeatedly dismissed resulting in a significant adverse effect on their mental health[16]. Failing to diagnose accurately and rapidly carries significant costs. In patients newly diagnosed with bile acid diarrhoea in secondary care, if the correct diagnostic test was requested at the first appointment (one in three patients), the episode of care costs £811.40 whereas if it was booked at a later appointment (two in three patients) the episode of care cost £1,568.31 and of course, delaying correct diagnosis means that patients have to put up with untreated symptoms for much longer[17]. Despite clear evidence that this diagnosis is frequently mistaken for IBS, the scan which accurately diagnoses bile acid diarrhoea remains significantly underused in the UK.

A systematic review investigating the prevalence of small intestinal bacterial overgrowth (SIBO) in patients diagnosed with IBS reported a pooled prevalence of 38% (95%CIs 33-46%)[11]. A systematic review of the frequency of pancreatic insufficiency misdiagnosed as IBS suggested a prevalence of 7.1%[5]. Systematic reviews of the efficacy of a low 'Fermentable Oligo-, Di-, Mono-saccharides And Polyols' (FODMAPs) diet or gluten free diets show that the overall quality of the data are very low and although there is benefit in some patients it is difficult as yet to quantify accurately how often carbohydrate malabsorptive syndromes and non-coeliac gluten sensitivity occur[8].

The symptoms produced by the conditions listed above are similar. In a prospective study, albeit in a different patient group, those with new onset gastrointestinal (GI) symptoms after cancer treatment, in whom conditions 5-9 are common, expert clinicians correctly predicted the underlying condition based on GI symptom assessment and history alone in only 24% patients. When more than one diagnosis contributed to symptoms, they never predicted the correct combination of diagnoses[18].

In a recently published randomised controlled trial (RCT) in the Lancet[19] a structured approach to investigating and managing 23 different GI symptoms following a defined checklist of investigations and management algorithms applied systematically was highly effective at improving symptoms. This was in patients with new GI symptoms developing after radiotherapy for pelvic cancer who required on average only 3 appointments and was relatively inexpensive. This was achieved in a condition widely considered to be complex or even untreatable. Furthermore, a trained nurse achieved benefits in most of this patient group, not inferior to those achieved by a consultant gastroenterologist[19].

The ability of nurses to develop skills sufficient to manage patients with specific conditions is unsurprising. Others have shown that 80% cure or improvement is feasible after interventions by specially trained nurses for patients with faecal incontinence. Chronic constipation, straining and evacuation difficulties can also be helped by nurse led treatment, and when patients are not cured, they nevertheless often report they are highly satisfied with their improvement and have greatly improved ability to live with symptoms[20].

In patients with IBS-like symptoms, there have been no prospective studies in primary or secondary care that have examined whether using a comprehensive panel of investigations for likely organic disorders is effective, how much it would cost and whether any health benefits are achieved. Nor has it ever been tested whether nurses following checklists could achieve results equal to or better than those achieved by GPs following NICE guidance.

Although active management of symptoms using algorithms has been tested in two studies in patients with IBS in secondary care, they have been limited in their scope, for example focusing on just one possible diagnostic test - faecal calprotectin[21] - or in second study, investigating a strategy of using endoscopy in addition to the NICE recommended tests. However, the investigations used would not have excluded many of the diagnoses listed above: particularly pancreatic insufficiency, bile acid diarrhoea, small bowel intestinal overgrowth or any carbohydrate malabsorptive syndromes other than lactase deficiency[22].

5. Hypothesis

In a common, often debilitating condition which is expensive for patients and healthcare, where no single treatment helps even a majority of patients, there are no reported studies which systematically look to see how many of the patients with IBS-like symptoms which include diarrhoea have one of the many possible organic conditions which produce the same symptoms.

This study will use checklists of investigations and apply treatments systematically, to explore whether patients with IBS-like symptoms characterised by predominant diarrhoea presenting in primary care, benefit from a rigorous management approach using well defined, mostly non-invasive and relatively cheap investigations to make a clear diagnosis of organic conditions which otherwise would be missed if the GP follows NICE recommendations.

The underlying hypothesis is that many patients confidently diagnosed using the ROME IV criteria as having diarrhoea predominant or mixed diarrhoea/constipation IBS in fact have treatable organic diagnoses which are currently missed due to inadequate investigation of GI symptoms.

6. Research question, aims and objectives

This study challenges current approaches following NICE recommended treatment options and assesses:

Research question: Is nurse-delivered structured care for patients with suspected IBS presenting to primary care clinically effective and cost-effective compared with usual GP care?

Research aim: To investigate the effectiveness and cost-effectiveness of nurse-delivered structured care (assessment, investigation using simple test and management of gastrointestinal (GI) symptoms) in patients with suspected IBS in primary care compared with usual GP care.

Research objectives

a) To investigate the effect of nurse delivered structured care for IBS patients on symptoms and quality of life.
b) To measure the cost-effectiveness of this approach from a health service perspective.

c) To undertake a process evaluation to explore the feasibility of training nurses to deliver structured care for patients presenting with IBS symptoms, and to understand the fidelity of delivery, contextual factors and barriers and facilitators to wider adoption.

7. Study end points

Primary end point
Improvement in patient symptoms at 1 year measured using the IBSSSS questionnaire

Secondary end points

- Economic evaluation of the healthcare and patient costs
- Change in quality of life at 1 year
- Time to symptom improvement
- Conditions diagnosed at any time from randomisation to end of 1 year follow up

8. Eligibility criteria

Inclusion criteria

- Adults ≥ 18 years old
- Able to read and understand English
- Able to give informed consent
- Presenting to primary care with GI symptoms that fulfil the Rome IV criteria for the diagnosis of mixed constipation/ diarrhoea IBS or diarrhoea predominant IBS (diarrhoea is defined as type 6 or 7 stools on the Bristol Stool Chart) for the first time in 5 years
- Taking no prescribed treatment for their symptoms

Exclusion criteria

- Patients not meeting the inclusion criteria
- Unexplained weight loss, rectal bleeding, fever, anaemia, palpable mass or sudden unexplained onset of symptoms
- Previous referral for chronic GI symptoms to a gastroenterologist or GI surgeon
- Previous cholecystectomy
- Previous gastrointestinal surgery of any type except appendicectomy, abdominal wall or femoral hernia repair or diagnostic laparoscopy without surgical intervention
- Past history of Inflammatory Bowel Disease, Coeliac disease, chronic liver or pancreatic disease
- Past history of cancer (except basal cell carcinoma)
- Consultation with any health professional in the last 5 years for abnormal GI symptoms.
- Previous investigations in secondary care for IBS-like symptoms
- Pregnancy at time of start of the study

9. Randomisation

Once eligible patients have signed the structured consent form, they will be randomised 1:1 to either usual following NICE guidance by the GP or a checklist of structured investigations

and management. The Hull Health Trials Unit (HHTU) will provide and maintain a purpose built, web-based data capture system with integrated randomisation. Following assessment of baseline outcomes, participants will be randomised 1:1, IBSSSS score (mild + moderate v severe) and patient gender (male v female). It is not possible to blind nurses or participants to the intervention but researchers analyzing data will be blind to treatment allocation. Access to the randomisation system is managed by HHTU staff and users are granted role-based access restricted to sites they are working at.

10. Study processes

Nurse training

Once the study nurses are recruited, they will undergo at least 6 weeks training which will be facilitated by the clinical members of the study team who will also offer ongoing regular support during the trial assisted by two senior nurses working in the community. The nurses will undergo a formal assessment of their competencies to manage the patients recruited for the study before the study opens.

Recruitment

Social media or posters placed in community pharmacies, GP surgery waiting rooms and other NHS healthcare settings may be used to alert the patients that this trial is ongoing However, to take part in the study, patients need to be referred to the study team by their primary health care team. Patients who present to the primary care team, seem to meet the eligibility criteria, and are interested in participation will be offered a patient information sheet about this study. After giving verbal consent that their details can be passed on to the research team, an email will be sent to the research team with the patients contact number and NHS number using NHS.net email addresses.

The research team will contact the patient at least 24 hours after they have been given the information sheet but within 5 working days and if they meet the eligibility criteria, have read the patient information sheet and wish to take part in the study, they will be invited to attend an appointment with one of the research team at their GP practice or by virtual consultation (as recommended by the Department of Health, whenever possible due to Covid-19 and will be asked to provide written consent which may be e-consent.

Following written consent, all patients will be asked to complete the following questionnaires

- Baseline economic questionnaire
- GSRS symptom score
- HAD (Hospital Anxiety and Depression Score)
- IBS Severity Score (IBSSS) questionnaire
- PHQ-12 SS score
- EQ5D3L
- SF12

Data of the patient's demographics will be recorded in all patients and include:

- Patient date of birth
- Gender
- Ethnicity
- Occupation
- Alcohol intake as recorded on the summary care record (if available)
- Body Mass Index

- Presence of other comorbidities
- Family history of Coeliac Disease / Inflammatory Bowel Disease (Crohn's /Ulcerative Colitis)/ Bowel cancer and if present which degree relative and at approximately what age was this diagnosed.

In addition, the participants in the trial will be given a questionnaire to complete in which they can enumerate their monthly financial outgoings resulting from their IBS-symptoms and/or consultations/ investigations. Patients will be able to complete these forms on line, over the telephone or on paper each month of the study and the patient will be asked which will be easier for them and if so, how would they like to complete these questionnaires. They will also be asked if they would like to receive a monthly reminder letter/ text/ email/ phone call each month of the study with the next questionnaire. Even if patients have been discharged from clinical follow up, they will be contacted two monthly for 1 year from the date of randomisation to record any health related costs secondary to their IBS symptoms.

The IBSSSS score (mild + moderate v severe) and patient gender (male v female) will be used to stratify the patients via the online randomization system provided by the HHTU.

Randomisation to the GP arm

If the patient is randomised to the GP arm, the research nurse will make a follow up appointment with the GP surgery. The primary care team managing patients will be given a laminated sheet, summarising NICE recommended management.

Randomised to nurse-led management

Patients will be assessed in the GP surgery or during virtual consultations as detailed above using a 5 step approach. If abnormalities are found at each stage they will be treated and the nurse will only move to the next step if after that treatment the patient has on-going symptoms. For each test listed below, treatment algorithms developed during the nurse training period will be provided detailing management of all possible abnormal results. Standard information sheets will be provided to patients for any condition diagnosed. If a test or treatment is not performed correctly it will be at the discretion of the Chief Investigator whether the test is to be repeated.

1st consultation and initial tests

- Assessment of dietary fibre / caffeine / alcohol intake (using validated questionnaires)
- FBC, U&Es, coeliac screen, CRP, vitamin B12, folate, ESR, TFTs and Vitamin D (if not previously checked in the last 3 months)
- Stool for: 1. Pancreatic Elastase-1; 2. Faecal Calprotectin; 3. FIT 4. Stool for microbiological culture
- Glucose hydrogen methane breath test

2nd line test

- A ^{75}Selenium taurocholic acid (SeHCAT) scan
- Fructose hydrogen methane breath test

3rd line

- Trial of low FODMAPs diet

4th line test

(These tests are unlikely to be possible during the Covid-19 epidemic, because of restrictions on endoscopy services but will be restarted if circumstances allow)

- Upper GI endoscopy with duodenal biopsies and Flexible sigmoidoscopy

Data handling and storage

The number of patient appointments and all investigations booked for patients participating in both arms of the study will be recorded using established electronic systems and patient notes.

Drug costs will be assigned using the NHS Tariff and/or BNF prices. Other costs will be calculated using NHS tariffs for 2020-2021.

A random sample of electronic records taken from patients randomised to both arms of this study will be assessed independently to check compliance with treatment protocols.

A trial specific data management plan agreed by the Chief Investigator, Sponsor, HHTU and statistician will be drafted to provide detailed instructions and guidance relevant to database set up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

All the information obtained about participants in the course of the study is confidential and will be held in accordance with the General Data Protection Regulation (GDPR 2018). Data will be entered into RedCap Cloud, a web-based electronic data capture system. The HHTU Information Systems team will work with the Chief Investigator to design the specification, build and validate the database, which will meet the required regulatory standards. Data are stored on dedicated RCC hardware in EU data centres (including real-time backup) managed by Amazon Web Services to industry standards outlined in ISO 27001, PCI DSS, SOC 1 - 3, FISMA, CIS, CSA, NIST and UK Cloud Security Principles. Data is encrypted at rest and in transit.

Personal data will be collected and processed only for the purpose of allowing the research team to communicate with patients regarding the project. Personal information will not be shared with anybody outside the study. The participants will be allocated a unique ID number. Any hardcopies of data will be maintained in a locked cabinet, separate from the participant database.

A selection of data will be checked against source documents at various timepoints throughout the study in adherence to HHTU's data monitoring plan. All essential documents including source documents will be retained for a minimum period of 5 years after study completion.

Only authorised research personnel will have access to the data collected in this study. They may also be looked at by representatives of regulatory authorities and by authorised people from the HHTU to check that the study is being carried out correctly. All will have a duty of confidentiality to research participants and personal identifiable data will not be disclosed outside the research site.

Access to the EDC system is managed by HHTU staff who will create users on behalf of the trial team. Users will be required to complete training and sign a terms of use document. Users are granted role-based access which will be limited only to the sites they are working at.

Anonymised data will be downloaded directly from RCC by authorised research staff for the purposes of reporting and statistical analysis. The anonymised data will be stored on secure network drive in a folder that is only accessible to authorised researchers. Researchers responsible for statistical analysis and reporting will not have authorisation to edit data. Only authorised statisticians will have permissions to download data.

The database will be 'locked' to obtain the final dataset after:

- trial completion (last patient, last visit)
- completion of coding and data entry
- all data queries resolved and the database updated, any serious adverse event queries have been resolved and the database updated
- trial team notified of date of lock

A copy of the final trial dataset and end of trial notification will be sent to the Sponsor before the randomisation list will be released to the study statistician to enable statistical analysis. A copy of individual site's data will be sent to that site.

A copy of the final trial dataset will also be archived by the HHTU and sent to the Chief Investigator. Other authorised researchers requesting access to the dataset for further research may apply through the CI. Applications will be considered in keeping with the publications policy which will be agreed by the Trial Steering Committee.

The HHTU use Box.com for collaborative cloud file storage. The HHTU Box instance is managed by the HHTU with access limited to HHTU staff and authorised members of the research team. Along will all trial documentation Box will be used for storage of interviews by researchers. Box uses EU data centres and complies with (and is independently audited against) the following standards:

- SOC 1, SOC 2 and SOC3
- ISO27001/270018
- Department of Defence Cloud computing Security Requirements Guide
- FedRAMP Level 4
- FISMA
- FINRA/SEC 17a-4
- HIPAA/HITECH

Box acts as a data processor only for the purposes of storage of trial data. Further details on Box data security and GDPR compliance is available here:
https://www.box.com/en-gb/security. The data protection risks of the HHTUs use of Box have been formally evaluated via a data protection impact assessment.

Patient recruitment

After the study opens, we anticipate that we will recruit 8-10 patients per month and we will require a maximum of 16 months for recruitment and a further 12 months for follow up. We anticipate that we will be able to report our data in abstract form within 2.5 years of opening the study and have a manuscript in press within 3 years.

11 Statistics and powering of this study

Design The null hypothesis is that the treatment in the nurses arm is not more efficacious than treatment by the GP

- Study: randomised controlled trial
- Parallel design
- Interventions: 2
- Outcome: IBS severity scoring system, 0-500 (Francis et al., 1997), Mild 75-175, Moderate 175-300, Severe >300
- Expected loss to follow-up: 10%
- Lost due to GP deviation from protocols: 15%
- Alpha: 0.05, 2 sided sd = 84.9000

Stratification

1. By gender (male v female)
2. They will be stratified by their baseline IBS SSS score into 2 groups: (a) mild or moderate (b) severe to ensure the arms are balanced for severity of symptoms.

Sample size

We assume 75% of participants will fall into the mild to moderate group (a) and 25% into the severe group (b). We anticipate that there will be a different effect size in each group so we will test them separately. A reduction in score of 50 is the minimum clinically important difference we aim to achieve. However, we also know that 50% of the control group will improve with NICE suggested treatments

The expected value of the primary outcome for the trial in the control group is 125.4 in the mild to moderate group, and 372 in the severe group. The standard deviation is 53.4 and 66.0 in the mild to moderate group and severe groups respectively. We have assumed that 5% of the control patients will be treated in a more similar way to the intervention group, leading to an inflation of the control group change in outcome measure. This makes a change in the difference between control and intervention of 47.5 that we wish to detect. Using a power of 85%, and alpha of 5% gives 72 in total from the severe group and 48 in the mild to moderate group. Each group is randomised half to intervention and half to control. After allowing for loss to follow-up of 10%, the severe group rises to 80 and the mild to moderate group to 54. Giving a total needed of 134 participants.

Stratification

Analysis

Means ± SD values or percentiles appropriate to the distribution will be reported for the primary outcome and secondary outcomes by treatment group. A statistical model will be fitted with IBS severity scoring system[23] as the dependent variable. This will be adjusted for baseline assessment of the IBS severity score. A random effects model will be explored. A point estimate, 95% confidence interval and p-value will be reported for the average treatment effect. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or robust statistical methods will be used instead.

Mixed linear regression models will be used to compare continuous outcomes between treatment groups by adjusting for corresponding metric calculated at baseline and random site effect.

For assessing group difference in demographic covariates, including age, sex and socioeconomic status, linear regression models will be used to compare continuous and ordinal variables, logistic regression will be used to compare categorical variables, and Poisson regression models will be used to compare event rates, while adjusting for a random site effect. For analysis of adverse events, formal statistical comparisons will only be performed when there are enough observed events. If outliers exist, a robust Poisson regression model will be used instead.

Missing data for secondary outcomes will not be imputed. Available case analysis method will be used for secondary analyses.

Two sided p-value will be reported and a 5% significance level will be used to declare statistical significance. For all above mentioned secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

A detailed statistical analysis plan will be drafted and approved by the Trial Management Group before data lock.

Subgroup Analyses
The study is not powered to detect subgroup differences. Interpretation of any subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. If performed the subgroup analyses will be conducted for the primary outcome and will be interpreted with caution.

Analysis Population
The analyses will follow the intention-to-treat principle. It will include all randomised participants, the data from whom will be analysed in the group to which the subjects were assigned through randomisation regardless of the actual group they ended in. Data will not be truncated due to protocol deviations.

Within-trial analysis
A separate statistical analysis plan will be drafted and approved by the Trial Management Group before commencement of the within-trial economic evaluation.

12. Process evaluation

In parallel with the clinical trial, A process evaluation of the study in line with MRC guidance[24] will be conducted.

Interviews with patient participants from each arm of the study after completing the intervention or comparison arm will be carried out. We will interview the trial nurses delivering the interventions and a sample of GPs in practices where the intervention is taking place. We will also audio-record intervention consultations to check fidelity.

The aim of these interviews is to explain the trial results and how best to scale the intervention, if it is shown to be effective, through the understanding of:

1. how the intervention is delivered to participants and its acceptability to them
2. how the intervention is communicated to participants
3. how the intervention was delivered by nurses and GPs, any protocol deviations and explanations for this.
4. the fidelity of the intervention over time
5. how participants respond to the any intervention suggested, how they interact with it, what they do as a result and any unexpected consequences;
6. any factors to do with families, friends, participants working environment, the GP practice or wider health service environment that affect intervention implementation during the trial, to try and understand the barriers and facilitators to intervention during the trial and help develop strategies to deal with this if the trial is successful and the approach is to be rolled out more widely.

The process evaluation will be delivered by a trained research assistant using semi-structured interviews either face to face, by Skype or over the telephone and will last for 30-60 minutes. Interviews will be digitally recorded and transcribed verbatim.

Maximum variation of variables across the sample is the goal. Once saturation is reached, i.e. the interviews are not producing new information, they will stop.

Both nurses delivering the intervention will be interviewed on two occasions, after they have seen 10 patients each and then again after they have seen 20 patients. Data collected will include their demographic data (sex, age, ethnicity, and level of education), questions about intervention delivery and fidelity (including any changes made), what went well/could have been improved in the training they received, and the response of the patient to the intervention. Contamination will also be considered, i.e. delivery of any aspects of the intervention to control patients.

Contextual (practice, other) factors will be explored which may act as facilitators or barriers to wider implementation with the intervention nurses and up to 5 GPs participating in the study. Data collected on these GPs will include demographic data (sex, age, ethnicity, highest qualification) including any additional psychological or mental health training in managing people with IBS, number of years working at the practice and if the research site is a training practice.

Up to 15 patients from the intervention arm and 5-10 from the control arm of the study will be interviewed. Patients will be selected for interview to maximise variation in attributes which may be relevant to how the intervention is perceived and how it may affect them, for example their age, gender, marital status, employment status, ethnicity and educational level. We will explore patients' concerns or expectations, understanding of the treatment, responses to the intervention and mechanisms by which outcomes are achieved.

Consent

For patients, this will be sought at the time of consent for the main trial. Participating GPs will be sent an e-mail or letter inviting them to participate in the interview by the researcher. They will be sent an information sheet and a consent form to either sign and scan back or return in the post prior to the interview. If there is no e-mail response after 2 attempts to contact them, they will not be approached further. Nurses delivering the nurse led arm will be ask to agree to participate in this process evaluation at time of interview and it will be stated in their job plan.

Analysis

Qualitative data from interviews will be analysed using framework analysis[25] based on the MRC recommended constructs[24] supported by NVivo. We will also assess intervention consultation audio-recordings using an intervention checklist.

13. Withdrawal

Participants may be withdrawn from the trial either at their own request and are not required to give a reason for this, or at the discretion of the Investigator. Patients who become pregnant, are diagnosed with a new malignancy, undergo abdominal surgery or have significant change in their health during the course of the study will be withdrawn. The participants will be made aware that this will not affect their future care. Participants may withdraw fully from the trial (from the intervention and from further data provision), or from the intervention only but continue to provide data. If the patient withdraws consent; reasons for withdrawal will be sought and recorded, whilst respecting the participants' right to give no reason. Participants will be made aware that should they withdraw the data collected to date will be retained and used in the final analysis.

14. Adverse events

We are not anticipating Serious Adverse Events as a result of the care pathway as this is a non-CTIMP (Clinical Trial of an Investigational Medicinal Product) study. However, all adverse events defined as those resulting in death, as being life-threatening, requiring hospitalisation or prolongation of hospitalisation, resulting in persistent or significant disability or incapacity to a study participant will be reported in line with sponsor's standard operating procedure for adverse events reporting for non-CTIMP Trials.

15. Regulatory & Ethics Committee Approval

The study shall not commence until the study protocol, information sheets and consent forms have been reviewed and approved from a Research Ethics Committee and relevant NHS/Social Care permission and Regulatory approval is obtained.

The sponsor will be responsible for deciding whether amendments are substantial and non-substantial in collaboration with the Chief Investigator. Where an amendment is required to study documentation that required REC approval, changes will not be implemented until REC approval and HRA categorisation is received. Where an amendment requires local approval this shall be sought prior to the amendment be implemented at each site in accordance with the categorisation given on the HRA approval letter. Should an amendment be required to eliminate an apparent immediate hazard to participants this may be implemented immediately and the REC/HRA and R&D will be notified as soon as possible.
Minor amendments for logistical or administrative purposes may be implemented immediately. Amendments will be logged on the Sponsor's Study Amendment Log and stored in the Trial Master/Site File(s).

Annual Progress Reports shall be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given – until the end of the study.

A final report shall (where possible) be submitted to the REC within one year after the end of the study.

If the study is terminated prematurely the CI will notify the REC, including the reasons for premature termination.

16. Assessment and management of risk

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

17. Peer review

This protocol has been internally reviewed by all members of the research team, members of the East Midlands CRN and lay representatives to assess the ethical aspects of this study and advice on scientific quality of the study. The initial application which is substantially the same as this protocol externally reviewed as part of the process for the award of funding by the NIHR Research for Patients Benefit funding stream.

18. Public & patient involvement

Patients have been actively involved in reviewing study documentation (PIS, CRF and study questionnaires). Patient and public representatives are members of the research team, advising on and supporting project progression and will help with preparing a lay summary of the study findings for dissemination.

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19. Protocol compliance

Accidental protocol deviations may occur at any time. Accidental protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, these will require immediate action and could potentially be classified as a serious breach

Accidental protocol deviations may occur at any time. Accidental protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, these will require immediate action and could potentially be classified as a serious breach.

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

In the event of a serious breach, the Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

20. Data protection and patient confidentiality

All study staff and investigators will comply with the principles of the Data Protection Act 2018 in protecting the rights of study participants with regards to the collection, storage,

processing and disclosure of personal information and will uphold the Act's/Regulations core principles.

Each participant will be assigned a study identity number, for use on all trial documents and the electronic database. Personal data, research data and the linking code will be stored in separate locations. When stored electronically, this will include using encrypted digital files within password protected folders and storage media.

Personal data will be stored for 1 year following the end of the study, so that the Chief Investigator may provide participants with a summary of the research (should they wish to receive a copy). Data generated as a result of this study will be available for inspection on request by the HHTU/Lincolnshire Community Health Services NHS Trust, the REC, local R&D Departments and the regulatory authorities.

21. Indemnity

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

22. Access to the final dataset

The full dataset for this study will only be accessible to the Chief Investigator. Archiving will be authorised by the Sponsor following submission of the end of study report. All essential trial documents including source documents will be archived in accordance with the a Data Handling Plan for a minimum period of 10 years after study completion. Destruction of essential documents will require authorisation from the Sponsor.

23. Dissemination and publication policy

The data custodian will be the Chief Investigator on behalf of Lincolnshire Community Health Services. Plans are made to disseminate the findings in peer-reviewed journals and conferences. All publications and presentations relating to the trial will be authorised by the Trial Management Group. Authorship and the order in which authors are listed will be determined by the Trial Management Group and will include the Chief Investigator, Co-investigators, Collaborators, and Trial Statistician. In addition any GP practice which contributes more than 20 patients to the study, will be entitled to nominate one GP as an author.

Authors will not present data at any time separately to the total data available, without the written permission of the chief investigator.

In line with the current guidelines of The International Committee of Medical Journal Editors, each member of the research team will be required to meet each of the following four criteria to be identified as an author;

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributors who do not meet all of the above criteria for authorship (despite being given the opportunity to) will not be listed as authors, but they will be acknowledged in any publication. Examples of activities that alone (without other contributions) will not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading.

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1. Appendices

Questionnaires to be used:

a) EQ-5D-5L
b) HADS score
c) IBSSSS
d) Modified PHQ 12 Questionnaire
e) Gastrointestinal Symptom Rating Scale
f) Baseline economic data questionnaire
g) Monthly economic diary
h) SF 12