IBD BOOST
Living well with Crohn's & Colitis

Identifying potential medical causes of fatigue, pain and urgency in inflammatory bowel disease and optimising medical management of these causes.

The IBD-BOOST OPTIMISE Study

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The study as detailed within this research protocol **(Version 7.0, dated 16.08.2022)**, or any subsequent amendments will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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ABBREVIATIONS / GLOSSARY OF TERMS

AE	Adverse Events
BCC	Barts Cancer Research UK Centre
CCUK	Crohn's & Colitis UK (registered charity supporting people with IBD)
CD	Crohn's disease
CRF	Case Report Form
CI	Chief Investigator
CV	Curriculum Vitae
FI	Faecal Incontinence
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
IRAS	Integrated Research Application System
KCL	King's College London
LNWH	London North West Healthcare NHS Trust
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PCTU	Pragmatic Clinical Trials Unit (Queen Mary, University of London)
PGfAR	Programme Grant for Applied Research
PI	Principal Investigator (local collaborator / lead at each research site)
PIS	Patient Information Sheet
PMG	Programme Management Group
PSC	Programme Steering Committee
PPI	Public and Patient Involvement
QMUL	Queen Mary's University of London
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAEs	Serious Adverse Events
SoA	Statement of Activities
SoE	Schedule of Events

UC	Ulcerative Colitis

STUDY SUMMARY

Short Title	**IBD-BOOST: OPTIMISE**
Methodology	A multicentre, non-randomised interventional study with 2 elements: 1. Self-completed checklist and postal faecal calprotectin sample 2. Review of checklist and if necessary review of the patient (telephone or clinic visit) by IBD nurse/other suitable trained staff to identify potential 'red flag' symptoms and/or active disease and other reversible causes for symptoms of fatigue, pain and urgency in people with Inflammatory Bowel Disease, according to a pre-developed algorithm. To manage any causes found according to the clinical algorithm. Process evaluation one to one online or telephone interviews with staff members carrying out the study for qualitative insights on intervention feasibility.
Research Sites	**NHS Trusts**: 1. London North West University Hospital NHS Trust (St Mark's Hospital) 2. St Helens and Knowsley Teaching Hospitals NHS Trust (Whiston Hospital or St Helens Hospital) 3. Dorset County Hospital NHS Foundation Trust (Dorset County Hospital) 4. Barts Health NHS Trust (Royal London Hospital)
Objectives/Aims	To screen patients with Inflammatory Bowel Disease who have indicated on a previous survey that they want help for fatigue, pain and/or urgency, to determine how many have potential medical causes of symptoms and to describe change in symptom scores after addressing those causes identified. To determine the feasibility of the IBD symptom checklist and algorithm in clinical practice and the costs incurred by the NHS, and additional qualitative process evaluation.
Number of Participants/Patients	200 patients
Main Inclusion Criteria	**Inclusion criteria** • Diagnosis of IBD (including patients with an ileo-anal pouch or stoma) • 18 years and over • Lives in UK and attends one of the IBD-BOOST clinical sites for routine IBD care • Has completed the IBD-BOOST survey (stage 2 of Programme Grant) and indicated that they would like further support to help manage their symptoms • Ability to give informed consent and sufficient command of English to understand study documents and procedures will be assumed from response to the previous survey **Exclusion criteria**

	• Under 18 years
Analysis	Statistical analysis to determine: 1. Proportion of patients with at least one potentially treatable cause for symptom/s (including active IBD disease flare-up). 2. For those receiving any test or intervention for a potentially treatable cause identified by the algorithm: change in symptom scores for fatigue, pain and incontinence will be estimated (at 3 months). 3. Proportion of people completing the checklist who have symptoms but subsequently decline suggested medical test or intervention (such as a blood test or medication). Health economics analysis to estimate (among participants undergoing medical optimisation): 1. IBD-related healthcare use and costs incurred for tests and subsequent interventions (NHS perspective) 2. Change in health-related quality of life (EQ-5D-5L utility) Qualitative analysis of process evaluation interviews with staff members (1 per site) carrying out the study for insights on feasibility and suggested modifications.
Proposed Start Date	1st June 2019
Proposed End Date	31st December 2022
Proposed follow-up end	31st March 2023
Study Recruitment Duration	43 months
Study Total duration	46 months

ROLES AND RESPONSIBILITIES OF COMMITEES/GROUPS & INDIVIDUALS

The Chief Investigator (CI) (Norton) has overall responsibility for the study.

The Programme Management Group (PMG), includes all co-investigators of the IBD-BOOST programme as well as the research team. The PMG and research team are responsible for the planning, execution, analysis and writing up the project.

Programme Co-investigators

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Mrs Imogen Stagg	Research Nurse	*London North West University Healthcare NHS Trust*
Dr Vari Wileman	Research Associate	*King's College London*

The Programme Steering Committee (PSC) has responsibility for advising the IBD Programme Management Group and providing oversight to the programme.

Programme Steering Committee Members

Dr Stephanie MacNeill (Statistician)	*University of Bristol*
Professor Ronan O'Carroll	*University of Stirling*
Dr Shaji Sebastian	*Hull & East Yorkshire NHS Trust*
Ms Katie Simpson (Chair)	*Patient Representative*
Ms Catherine Stansfield	*Salford Royal Hospitals NHS Foundation Trust*
Mr Kamil Sterniczuk	*Patient Representative*
Mr Peter Wheatstone	*Patient Representative*

Sponsor Representation to PMG and PSC

Sunder Chita	Health Service Research Manager	*London North West University Healthcare NHS Trust*

Patient & Public Involvement (PPI): responsible for contributing to development of the checklist and algorithm and all patient-facing materials.

PROTOCOL CONTRIBUTORS

The funder will play no role in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The funder will not control the final decision on any of these aspects of the study. Patients with IBD have been involved in designing the study including designing all patient-facing materials.

KEY WORDS: Inflammatory Bowel Disease; Crohn's disease; ulcerative colitis; fatigue; pain; faecal incontinence; urgency

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1. BACKGROUND

Inflammatory Bowel Disease (IBD) affects 300,000 people in the UK (https://www.crohnsandcolitis.org.uk/about-inflammatory-bowel-disease), causing unpredictable bouts of gut inflammation, with acute illness, diarrhoea, and pain. In remission, many people with IBD live with fatigue, chronic pain, and bowel urgency/incontinence (1). There is no current cure for IBD, which usually starts in childhood or as a young adult. Most previous IBD research has focused on controlling inflammation. However, many people report continuing IBD-related fatigue (41%), abdominal pain (62%) and difficulty with continence (up to 75%) even when IBD is in remission (1-3). These symptoms limit peoples' quality of life and ability to work and socialise. Patients feel these symptoms are not taken seriously by health professionals and report that little help is given (4-6). However, the James Lind Alliance IBD research priority-setting consensus put fatigue, pain, and continence in the top 10 issues that IBD patients and clinicians want to be addressed by research (7).

1.1 The IBD-BOOST programme of research

The current application is stage three of IBD-BOOST, a National Institute of Health Research (NIHR) Programme Grant for Applied Research (PGfAR) funded programme. The overall aim of the Programme Grant is to improve the quality of life of people with IBD by reducing the burden of IBD-related fatigue, pain, and urgency/incontinence. See Appendix 1 (page 25) for an overview of the whole IBD BOOST programme.

The current protocol is for stage 3 of the programme, a non-randomised interventional study to test a checklist and algorithm for identifying and managing potential medical causes of these IBD-related symptoms.

Stage 1 of the programme involved focus groups and interviews with people with IBD and IBD nurses to inform the development of the checklist and algorithm under investigation in this study. This study was undertaken with REC Approval (REC reference: 17/WA/0349/ IRAS number: 228902). Data from this stage has also been used to develop an online self-management intervention which will be hosted on an electronic platform.

Stage 2 of the programme involves a large cross-sectional survey to people with IBD to investigate the inter-relationships of these IBD-related symptoms and the proportions wanting support to manage these symptoms. This survey protocol has been approved by an Ethics committee (REC reference: 18/NW/0613/ IRAS number: 246185). Survey participants who consent to be contacted for further stages of our research, and who attend one of our clinical sites for their routine IBD care, will be invited to participate in the Optimise Study (this stage) and then, if eligible, will later be invited to participate in the RCT.

Stage 3 (this project) of the programme is a non-randomised interventional study to test a checklist and clinical management algorithm which we have developed within this programme for identifying and managing the most common medical causes of these IBD-related symptoms. We will then address any medical abnormalities detected. Participants who have no medical causes identified by the checklist and algorithm, or who have abnormalities and complete this medical optimisation but have continuing symptoms after medical optimisation will then be invited to take part in an RCT of online self-management. The RCT will also be offered to eligible people declining participation in the present study, or who consent to the present study and complete the checklist but who subsequently decline any suggested medical test or intervention.

Stage 4 is a Randomised Controlled Trial (RCT) of online self-management for these symptoms, with an embedded pilot study, a study within a trial, a health economics evaluation and process evaluation. Potential participants will already have completed the stage 2 and possibly stage 3 of the IBD-BOOST programme of studies.

1.2 Rationale

These symptoms of fatigue, pain and urgency/incontinence have a major impact on quality of life in people with IBD, but have been largely ignored by clinicians and researchers. Our programme, shaped by the concerns of our patient and clinician stakeholders, focuses on a supported online self-management intervention for these symptoms. The checklist and algorithm stage (this study) will help identify participants who will be suitable for a self-management intervention and ensure that anyone displaying "red-flag" symptoms (indicating an urgent or serious medical issue) is identified for prompt treatment. It is currently unclear how useful it is to investigate these symptoms and whether symptoms will respond to correcting biomedical abnormalities.

1.3 The need for research

It is currently unclear how best to manage these common symptoms of fatigue, pain and urgency/incontinence in people with inflammatory bowel disease. Many patients do not report these symptoms at all, or if they do are offered little beyond investigation and treatment of active disease. We have found in previous work that many patients do not receive what are considered "standard care" investigations or management for these symptoms (8).

Our previous systematic literature reviews (9-12) have identified many potentially reversible causes for these symptoms. Many of these, particularly the psycho-social elements, will be addressed in our online self-management programme which follows on from the current proposal within our programme grant. However, there are also "medical" causes (such as anaemia as a cause of fatigue), which could be addressed before patients enter a self-management programme. However, during extensive consultation with expert clinicians during development of the current checklist and algorithm, there is genuine equipoise over whether patients need these medical causes addressing, whether it is likely to make any difference to symptoms, or whether they should be able to directly access online self-management (the RCT in the next stage of our programme).

1.4 **Development of the checklist and algorithm**

Our development work for this study has involved consulting a wide variety of gastroenterologists, IBD specialist nurses, patients and others. This work suggests that there is no current "standard of care" for investigating and treating these symptoms. Some clinics do very little while others conduct many different tests, with little consideration of costs or inconvenience to patients.

Over an extensive series of interviews and group activities with stakeholders, we have now developed consensus on the contents of an algorithm for investigating and managing symptoms of fatigue pain and urgency/incontinence, with an accompanying preliminary self-completed checklist. During this development we have focussed on the common evidence-based causes (from our systematic reviews above) and interventions for our three symptoms (fatigue, pain, urgency), which consultees felt were also feasible for implementation in routine clinical practice. We have tried to achieve a balance between feasibility, costs and

completeness. There were many other candidate tests, which were either not evidence-based or that patients and clinicians felt were too onerous to be part of routine clinical care for all patients with these symptoms.

The IBD-BOOST Algorithm (Appendix 3) and preceding patient-completed Checklist (Appendix 4) are a pragmatic algorithm for detecting and treating the most likely/common causes for symptoms (based on the evidence base in the literature reviews above). It is intended to be suitable and feasible for implementation by IBD nurse specialists or other IBD clinicians (or GPs outside of this study) in their routine everyday practice. It therefore consists of "red flags" (the clinical conditions that are considered essential to know and that would potentially make self-management dangerous), and disease activity via a simple test (faecal calprotectin) and a self-report questionnaire (IBD-Control)(13). If there are no red flags and IBD is apparently in remission, only the most common evidence-based causes for symptoms of fatigue, pain and urgency considered essential by clinicians and patients during our development work, are then explored. Nurses and other clinicians who will implement the algorithm at our clinical sites will receive a face to face or online training session and a training manual for reference on how to use the checklist and algorithm.

The nurse/clinician will initially review the patient's responses to the checklist, the result of a faecal calprotectin test and the medical notes and decide if the patient is clearly in remission and has no "red flags" or other issues which need investigating, according to the algorithm. Some participants will at this point clearly have no need for further action and be eligible for entry into the RCT for self-management (separate to the current application). Others will need a follow up phone call to clarify some issues, or need a face to face review with the nurse/clinician, or immediate onward referral to medical colleagues (if they have "red flags" which warrant urgent medical attention).

Depending what these enquires reveal, the nurse will then initiate appropriate management for any abnormalities found which may be causing symptoms (such as active IBD disease or anaemia). If tests or new management are initiated, the nurse will determine, using clinical judgement, whether to see the patient face to face or follow up via telephone or email. S/he will review the patient or the results of tests as necessary and decide when the patient's symptoms have been "optimised", over the following 3 months, while recognising that in IBD not all biomedical abnormalities and disease activity may be resolvable. The management initiated will be standard care treatments (as agreed during our consensus process) and not any novel interventions outside of standard care. Tests ordered, their results and management initiated will be recorded after each activity on a study Case Report Form (CRF) (Appendix 5; IBD-BOOST Medical Management Optimisation CRF).

2. OBJECTIVES

2.1 Primary research question:

I. Of those people with IBD who experience fatigue, pain and/or faecal urgency/incontinence and express an interest in intervention for one or more of these symptoms, what proportion have patho-physiological contributors which are potentially medically treatable?

2.2 Secondary research questions:

I. Is implementing this checklist and algorithm feasible in routine NHS clinical practice?
II. In patients with symptoms and potentially reversible medical causes do these symptoms change at 3 months after initiating algorithm-led management? Note: the design of this study will not allow inference of causality of symptoms.
III. In patients starting algorithm-led management, what NHS resources are used during the implementation of the algorithm?
IV. In patients starting algorithm-led management, what change is observed in health-related quality of life (EQ 5D 5L utility)?
V. What is the experience of nurses implementing the Optimise algorithm and what are their suggestions for any changes to enable future NHS implementation (via qualitative interviews)?

This study also aims to identify and prepare potential participants for a future RCT of an online symptom management intervention. Participants who are not found to have any potentially treatable patho-physiological contributors will be invited to take part in the next stage of the programme, an RCT of an online self-management intervention. Participants who are identified as having potentially treatable contributors but have not experienced resolution of symptoms after three months of following the algorithm and want further help with symptoms will also be invited to the RCT.

3. STUDY DESIGN

This is a non-randomised interventional study to identify and prepare participants for the subsequent RCT which will follow. Potential participants will have already been identified via a survey in stage 2 (REC reference: 18/NW/0613/ IRAS number: 246185), as having symptoms and wanting help for them, as well as receiving their routine IBD care from one of our participating NHS trusts.

Those participants expressing a desire for help with symptoms and giving permission for future research contact when completing the survey will be sent a link to an online version of the checklist (Appendix 4) with up to 2 reminders by email or text message for non-responders. Alternatively, the checklist can be sent by post, the participant will receive a letter with information sheet, consent form, checklist and stamped addressed envelope. The checklist will be self-completed by the participant. The checklist also has a section measuring symptom severity and IBD control using validated measures. Participants consenting to the study and returning a completed checklist will then be sent a kit for a postal stool sample for faecal calprotectin to be sent to a central laboratory. This is to detect active IBD disease and forms a step in the algorithm for assessment of active disease.

The central team will alert clinical sites when one of their patients completes the checklist and faecal calprotectin test (permission for this is outlined in the participant information sheet and consent form). The checklist will be sent to the clinical team within 10 working days of the central study team receiving the completed checklist. An IBD nurse or other member of the clinical team (trained in using the checklist and algorithm) at the corresponding NHS site will then review the checklist and result of the faecal calprotectin test for any red flags and potentially reversible causes with reference to the algorithm (Appendix 3). A telephone call or clinic visit may be used for clarification of any unclear element.

If nothing further needs to be done according to the algorithm (patient is in remission and no further tests or management is indicated), the participant will be informed of this, thanked for their participation by letter/email (Appendix 14). They will be offered the RCT if they have consented for further research contact and are eligible for the RCT. If active IBD disease or any other of the issues in the IBD-BOOST algorithm are identified, the IBD nurse/clinician will initiate management based on the algorithm.

If a participant is clinically unwell, with a plan to change their IBD management at the time of their checklist being reviewed, their study participation should be paused. The participant should be informed of this pause in their participation via email/letter (Appendix 15) and a new checklist should be re-sent to them 6 months later via post or email. This new checklist should then be used to follow the algorithm. Participants will also complete a new faecal calprotectin sample at the same time as completing the new checklist.

Participants will have completed measures of symptom severity and IBD control when completing the checklist. If intervention is indicted by the algorithm, they will complete the patient reported outcome questionnaire (Appendix 6) at 3 months after return of both the checklist and faecal calprotectin test (only for those for whom the checklist indicates an abnormality which the algorithm addresses). Nurses will keep a record of their interactions with patients (phone calls, emails or clinic visits), tests ordered, results and interventions using a case report form (Appendix 5).

4. STUDY POPULATION

Adults with IBD who have completed the IBD-BOOST survey at stage 2 of our Programme Grant (REC reference: 18/NW/0613/ IRAS number: 246185) and have indicated on that survey that they would like further support for their symptoms. Those completing the survey who consented to being contacted for further research will be invited. The previous survey includes diagnosis, age, current country of residence, symptom scores and whether they would like further support. From this, the central research team will be able to ascertain who is eligible to be invited to participate in Optimise from participating clinical sites.

4.1 Inclusion criteria

- Diagnosis of IBD (including patients with an ileo-anal pouch or stoma)
- 18 years and over
- Lives in UK and attends one of the IBD-BOOST NHS clinical sites for routine IBD care
- Has completed the IBD-BOOST survey (stage 2) and indicated that they would like further support to help manage their symptoms
- Ability to give informed consent and sufficient command of English to understand study documents and procedures will be assumed from response to previous survey

4.2 Exclusion criteria

- Under 18 years

4.3 Sample size

From the prevalence of symptoms, we anticipated that at least 50% of 6,300 predicted respondents to the survey (stage 2) would report one or more symptoms of fatigue, pain or

urgency/faecal incontinence (n=3,150 symptomatic people). Of these, we anticipated approximately one third expressing an interest in further management for symptoms and attending one of our clinical sites for their routine IBD care, so approximately 1,000 people available as potential recruits for the present study. Of these, we anticipated 50% (500) would consent to recruitment to the present study. However, as a result of the impact of the Covid-19 pandemic on recruitment we have needed to reduce our overall sample size target from 500 to 200 participants, and the study will now focus on checklist and algorithm feasibility and descriptive statistics. With this sample size the width of the 95% confidence interval (CI) for the proportion of participants who have patho-physiological contributors which are potentially medically treatable would be at most 13.9% (normal approximation CI).

4.4 Identifying and Recruiting Participants

Potential eligible participants will be identified by the central study team, based on responses to the previous Ethics-approved survey indicating presence of symptoms and desire for intervention. Survey respondents who are receiving clinical care at one of our study clinical sites will be identified by the central team (if they have given consent for future contact). For the purposes of eligibility for the Optimise study, a completed survey (previous study) will be defined as having the following fields completed (number relate to previous survey items):

- Part 1: contact details
    1. First Name
    2. Surname
    3. Phone number
    4. Email address
    5. Postal address (required for calprotectin, and to check UK residence)
    11. NHS site
- Part 2: your IBD and your health
    1. Which of the following have you been diagnosed with?
        a) Crohn's disease
        b) Ulcerative Colitis
        c) Other form of inflammatory bowel disease
- Part 3 Symptoms;
    a. At least one section (Pain, Fatigue or Urgency) complete.
- Part 8
    1. Gender
    2. Age in years
    3. Ethnicity

Potential Optimise participants will be sent a Participant Information Sheet (PIS) (Appendix 7) and will consent to the current study either via a link emailed or via a paper consent form posted to them by the central team (Appendix 8 for invite email: one reminder if no response is received; Appendix 9 (consent form paper copy/online copy). Those consenting will then receive a subsequent link to the online checklist. If consenting via post a paper copy of the checklist will be sent with the PIS and consent form. There will be two reminders by email or text for those consenting but not returning the checklist after one and three weeks (see Appendix 10).

Responders completing the checklist will receive a postal kit for a stool sample, to be posted to a central laboratory for analysis of faecal calprotectin levels as an indicator of disease

activity. There will be two reminders by email or text for those receiving a stool sample kit but not returning it at 2 weeks and 4 weeks after being sent (Appendix 10).

Checklists will be sent to the sites teams once completed in order for the clinical team to act on any responses to the checklist which may require urgent attention. Once the calprotectin results are received, the central team will again notify the relevant clinical site for that participant and pass on the faecal calprotectin test results for clinical review using the algorithm. This transfer of personal data is clearly outlined in the PIS and consent for this is included on the consent form. A copy of their calprotectin results will be emailed to participants from a secure NHS email address along with an explanation that it will be passed on to their care team: (Appendix 12).

5. CONSENTING

Written information about the study (Appendix 7) will be emailed or posted to potential participants. Participants will be able to participate by providing consent via a paper consent form (Appendix 9) or via an online link (Appendix 8) emailed to them by the central team.

The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw from the study at any time without giving reasons and without prejudicing further treatment. Their right and access to their usual NHS treatment will not be compromised in any way if they do decline to participate or withdraw. In line with GDPR guidelines, participant rights to access, change or move their information will be limited, as we will need to manage information in specific ways in order for the research to be reliable and accurate. If a participant chooses to withdraw from the study, we will keep the information that we have already obtained and no further information or data will be collected. To safeguard participant rights, we will use the minimum personally-identifiable information possible. All study participants will notify the Chief Investigator and lead research team based at King's College London if they wish to withdraw, using the contact details provided in the patient information sheet for the study.

6. DATA COLLECTION

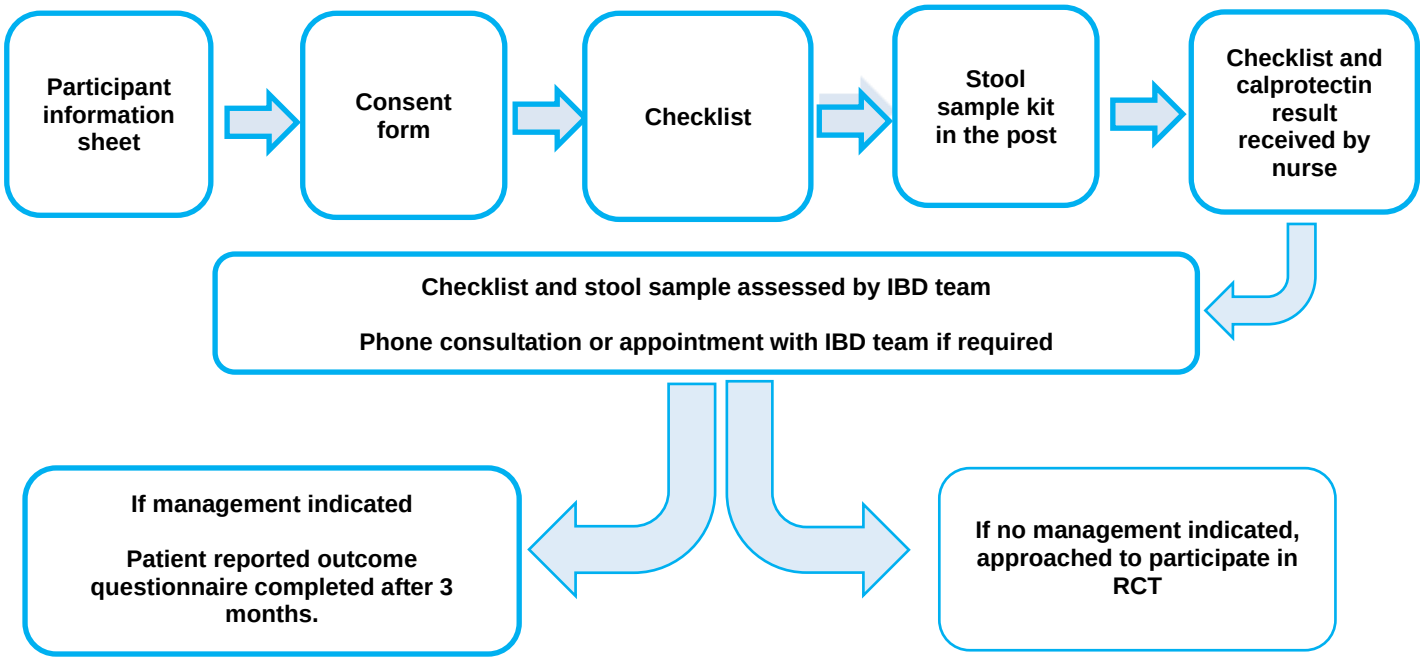
The checklist (Appendix 4) and outcome measures at 3 months (Appendix 6) will be self-administered. Participants will be invited to complete these through an online link provided or via paper copies sent to the study research team and stored at King's College London or LNWUH Trust. Data from the online version will be directly inputted into the database by participants. Paper copies received in the post will be inputted manually into the database by the research team.

Results for calprotectin tests on stool samples provided by the participant will be accessed by the central research team on King's College Hospital laboratory's secure results portal and uploaded on to the study database on the Calprotectin CRF (Appendix 11). Once the checklist and algorithm data are both available the participant's usual care clinical site will have four weeks to review and contact the participant.

If the checklist indicates an abnormality which the algorithm addresses, the participant will be sent the patient reported outcomes questionnaire (Appendix 6) at 3 months after the IBD nurse has reviewed the checklist. The questionnaire contains measures on symptom and IBD control repeated from the checklist and measures of quality of life also used in the IBD-

BOOST survey. Those who require a 3 month follow up will be sent this via email/letter and will be sent up to 2 reminders by email or text message for non-responders (Appendix 10).

6.1 Data Collection Flow Diagram



6.2 Outcome measures

Primary outcome measures

Proportion of participants with any of the following detected via the checklist, faecal calprotectin test or by the nurse/clinician following the algorithm (recorded on the Checklist, Appendix 4 & Optimisation CRF, Appendix 5):

- "Red flags" on checklist which require investigation
- Active disease (defined as faecal calprotectin 200 or over and/or IBD control score 13 or under)
- Abnormalities detected on blood test in people with fatigue
- Irritable Bowel Syndrome or functional dyspepsia diagnosed in people with pain (by responses on checklist)
- Untreated loose stool detected in people with urgency

Secondary outcomes

- Proportion of participants for whom a clinical intervention was indicated
- Proportion of participants who declined a suggested clinical intervention at consultation
- The cost of implementing the algorithm (clinical tests or intervention and nurse/clinician time to implement the algorithm)
  The checklist (Appendix 4) also includes the following measures, which will be repeated at 3 months (Appendix 6):

- PROMIS Short Form v1.0 – Fatigue 4a; 4 item validated scale to measure fatigue (14)
- PROMIS Scale v1.0 - Pain Intensity 3a; 3 item validated scale to measure pain (14)
- PROMIS Scale v1.0 – Gastrointestinal Bowel Incontinence 4a; 4 item validated scale to measure bowel control (15)
- IBD-Control score; 8-item self-reported score to measure disease control from the patient's perspective (13)
- EQ-5D-5L (Quality of Life measurement); a 5-item standardised measure of health (16)

Only those participants needing interventions as indicated by the algorithm, will be sent the outcome questionnaire (Appendix 6) at 3 months after return of the initial checklist and stool sample. This questionnaire will also include a free text feedback option at follow up to capture qualitative comments about the experience of completing the checklist and algorithm, and how onerous or helpful this was.

In addition, the nurse/clinician will complete the Optimisation CRF for each participant (Appendix 5), this will include number of visits or telephone contacts, all tests and results and all management initiated within the algorithm. Qualitative comments on taking the participant through the process of using the checklist and algorithm will be collected here.

Feasibility outcomes will include number consenting but then discontinuing (with reasons if possible), completion of outcome measures, completion of CRFs.

Process evaluation interviews

Due to having a reduced overall sample size (from 500 to 200 participants), a result of the impact of the Covid-19 pandemic on recruitment, the study will now focus on intervention feasibility. In order to try to establish whether implementing this checklist and algorithm would be feasible in routine NHS clinical practice, and what factors impact this, we will conduct telephone or Teams/Skype interviews with NHS clinicians (1 per site) who worked on the IBD-BOOST Optimise study.

Interviews will be completed to understand experiences of the using the checklist and algorithm, their acceptability, which aspects were most or least helpful, and the feasibility of implementing their use in routine NHS clinical practice, as well as any suggestions for improvements/changes.

Staff members working on the study will be contacted by the central team using the information leaflet (Appendix 16). Those indicating willingness will be interviewed using a topic guide (Appendix 17). The data will be analysed iteratively and as the interviews progress the topic guide will be adapted, based on themes which emerge from earlier interviews, to enable exploration of issues which appear relevant in later interviews.

All interviewees will be read the consent form questions by the interviewer (telephone or Teams/Skype interviews) and agreement to each statement will be audio recorded. Appendix 18 gives the consent form for NHS staff interviews.

Analysis: Interpretive data analysis will be informed by the Analytical Hierarchy Framework (AHF) (17), guiding methods for handling, analysing and generating findings from qualitative

data. This generic framework is appropriate for exploratory qualitative work as it guides the process of analysis through basic organisational data management stages, to descriptive and finally interpretive levels. The AHF acts as a set of instructions for progression through analysis; the specific detailed method of analysis is achieved through simultaneous use of a specific coding frame as part of that process.

Early findings will be collated, with new items identified in the first-round analysis being added to the coding frame. The research team will then conduct a second analysis using the enhanced coding frame. This iterative process can be repeated as required to ensure a thorough and robust analysis of the data. NVivo software will be used to manage data and enable sorting, labelling and retrieval of data segments prior to the human endeavour of interpretation and representation of findings.

6.3 IBD-BOOST Study Schedule

IBD-BOOST OPTIMISE		Within 1 week of completing checklist	Within 10 weeks of consent/ 2 weeks of trial team receiving the calprotectin result	Within 4 weeks of checklist and calprotectin data sent to clinical team	Within 3 months of checklist and calprotectin result reviewed	3 months after checklist and calprotectin result reviewed	Before study closure
Time Point	T0	T1	T2	T3	T4	T5	T6
Screening and invite sent	**X**						
Participant Information Sheet	**X**						
Consent Form	**X**						
Checklist	**X**						
Stool sample kit sent to participant		**X**					
Calprotectin result received and uploaded by central research team			**X**				
Checklist and calprotectin result reviewed by patient's local IBD team				**X**			
Medical Management Optimisation (if required)					**X**		
Participant reported Outcome Questionnaire completed (only if management provided)						**X**	
Clinician Qualitative Process Evaluation Interviews							**X**

6.4 Faecal Calprotectin tests

Faecal Calprotectin results will be obtained by posting sample kits to participants after the checklist has been completed. The kits will include a standard and widely used faecal sample pot, and packaging and postage will be compliant with 2004 Human Tissue Act. The envelope will have pre-paid postage. The pot sample will be labelled with the participant's study ID only. No identifying information will be sent to the laboratory at King's College Hospital. All samples will be disposed of following analysis. A copy of their result will be

emailed to the participant from a secured NHS email address within 3 weeks of receiving the sample along with an explanation and confirmation that it will be passed on to their IBD team (Appendix 12).

7. DATA ANALYSIS, MANAGEMENT AND PROTECTION

7.1 Data analysis

The percentage of patients requesting help with their symptoms who report at least one treatable cause will be estimated. The percentage of patients with each treatable cause will be estimated among all those seeking help. For those receiving intervention, change in fatigue, pain and incontinence scores will be estimated with confidence intervals.

The change in generic health-related quality of life (EQ-5D-5L) from survey to end of optimisation and the cost of implementing the optimisation algorithm will be evaluated.

We will collect data on all significant health (NHS perspective) resource inputs associated with optimising medical management. This will include hospital visits, diagnostic procedures, medication. The intervention-specific cost (email, telephone contacts, and tests) will be calculated based on the records (by nurses and doctors) of their interactions with patients. Unit costs from national sources will be applied to estimate patient-level total healthcare costs.

Free text comments from participants gathered in the questionnaire at 3 months (Appendix 6) and from nurses/clinicians (Appendix 5) will be subjected to a simple thematic analysis to determine views on feasibility and any changes suggested.

7.2 Data management

Live data will be stored on a secure database held by the Pragmatic Clinical Trials Unit (PCTU), Queen Mary University of London. Participants completing the checklist and outcome measure via an online link will input their data directly into the database. Paper copies will be received and stored securely at the central research team office or another designated office at King's College London or at LNWUH Trust. Pseudonymised data will be stored for 10 years as per the sponsor's requirement and then securely destroyed. This is stated in the PIS.

All interviews will be digitally recorded, anonymised, professionally transcribed verbatim and analysed using, if appropriate, NVivo8 software for data management. The interview data will be analysed by the qualitative researchers independently in researcher's offices and at the University site (King's College London). Anonymised transcripts will be stored on a password protected computer at King's College London. Audio files will be sent via the KCL secure file transfer service to a KCL approved transcriber who will delete their copy of the audio file and the electronic transcription once the latter has been returned to the research team. The transcriber will remove all identifiable data and render the interviews anonymous. Participants are advised of this in the Participant Information Leaflet. All original and transcribed interview data files will be password protected on computers (e-copies) and physically filed (hard copies) in a locked cabinet at the University site.

Audio files of interviews will be deleted at the end of the programme (planned for November 2023) and confirmation of destruction will be recorded. All other data arising from this study electronic or paper format will be kept for a period of ten years for data management governance as required by the sponsor.

7.3 Data protection and confidentiality of participants

The online checklist and outcome measure will be administered on the REDCAP system or by paper copy and then inputted manually by the central research team. Queen Mary University of London's London Barts Cancer Research UK Centre (QMUL BCC) IT Security is responsible for the security of the QMUL REDCAP service. Any data entered is securely stored at PCTU safe haven (BCC) in their Enterprise level data centres. Data will be backed up daily. Access to the system for data entry staff requires a user account, which will be issued and controlled by the PCTU Data Management Team. All data analyses will be conducted using only the unique study ID. Transfer of data will occur through strong encryption.

Data from the IBD-BOOST Optimise study may be used to support other research (in line with the applicable national regulatory standards) in the future and may be shared anonymously with other researchers as stated in the PIS and consent form.

8. ETHICS

8.1 Ethics favourable opinion, HRA approval and NHS R&D

The Chief Investigator will obtain approval from a recognised NRES Research Ethics Committee & the Health Research Authority (HRA). The study must be submitted for assessment of capacity and capability at each participating NHS Trust using the HRA/REC approved study document set and Statement of Activities (SoA) & Schedule of Events (SoE). The Chief Investigator will require a copy of each participating site's confirmation of capacity and capability, agreed statement of activities, PI & research teams current CV and GCP certificates, before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1996 (including later revisions) and any other relevant ethical guidance.

8.2 Amendments

On obtaining a favourable ethical opinion and HRA approval, any subsequent changes to the study conduct, design or management will be notified to the original approving REC & HRA and any other relevant regulatory authority via the UK Amendment process (http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/). Authorisation will be sought from the study Sponsor for any future substantial and non-substantial amendments arising during the course of the study, prior to submission to the relevant Research Ethics Committee and HRA. Changes to the study will not be implemented until REC/HRA approval has been obtained unless the clinical need warrants this, for example when urgent safety measures are required. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended. NHS R&D Amendment continuation of capacity and capability will be sought (where applicable) from the participating sites before any substantial changes can be implemented at the applicable site. Details of consent procedures are addressed above. An annual progress report will be submitted to the Sponsor and the approving REC/HRA by the CI.

9. STUDY CONDUCT RESPONSIBILITIES

9.1 Assessment and management of risk

This study has been assessed by the Pragmatic Clinical Trials Unit (PCTU) at Queen Mary University of London (QMUL) and it has been found to be a low risk study, as all care will be given by the subject's routine clinical care team and there are no tests or interventions suggested in the algorithm that are not part of routine clinical care. There is potential for participants to become distressed when thinking about their symptoms: the previously completed survey includes a link / website address to Crohn's & Colitis UK who provide support via their helpline, and contact details are included in the Participant Information Sheet. Whilst we do not expect any adverse events to occur in this study, in the unlikely event that any do occur the appropriate reporting procedures will be undertaken and followed up accordingly (see below Section 9.7).

The study will be entered for adoption on to the National Institute for Health (NIHR) Portfolio. All participating sites will be required to follow any applicable procedures outlined by the NIHR and PIs are responsible for uploading recruitment figures in the specified recruitment reports to the Chief Investigator's designated Data Support Coordinator.

9.2 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will work in accordance with the Caldicott Principles, Data Protection Act 2018, NHS Code of Confidentiality and any relevant NHS Trust organisational policies or Data Protection legislation. Participating NHS sites will be bound to act in accordance with these applicable regulations.

9.3 Indemnity

The Study is sponsored by the LNWUH NHS Trust; the NHSLA Indemnity scheme will cover the study.

9.4 Sponsor

LNWUH NHS Trust will act as the Sponsor for this study and will adhere to the UK Policy Framework for Health & Social Care Research 2017 and any amendments or subsequent replacements. Delegated responsibilities will be agreed with participating NHS Trusts via the statement of activities.

9.5 Funding

The study is funded by the NIHR Programme Grants for Applied Research funding stream.

9.6 Audits and inspections

As this is a low risk study, there will be no planned monitoring for sites. However, where there are any deviations or breaches to the study protocol or research procedures or other concerns for a site, triggered monitoring visits may be conducted at the CI's request by the Quality Assurance team at the PCTU at Queen Mary's University of London. Participating

NHS sites are required to comply with any requests for monitoring by the PCTU or the Sponsor or applicable site R&D Office and ensure that the study documentation and information is available. Copies of audit / monitoring reports should be sent to the Sponsor's R&D office. Protocol deviations, non-compliances, or breaches from the approved protocol must be reported immediately to the Sponsor R&D Office.

9.7 Safety

Adverse events (AEs): AE are any clinical change, disease or disorder experienced by the participant during their participation in the study, whether or not considered related to the use of the intervention being studied.

Serious adverse events: An AE is defined as serious (an SAE) if it results in one of the following outcomes:

- A life-threatening AE
- In-patient hospitalisation or prolonged hospitalisation not related to IBD flares, which are expected events
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect in the offspring of a subject
- Is otherwise considered medically significant by the investigator
- Other medical events requiring intervention to prevent one of the above outcomes.

Follow-up after SAEs: An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator (CI) the event was:

- Related – that is, it resulted from administration of any research procedures and
- Unexpected – that is the type of event is not listed in the protocol as an expected occurrence

The Chief Investigator or Sponsor will complete and send a SAE report for non-ctimps (clinical trial of investigational medical products) to the REC within 15 days of becoming aware of the event.

After a SAE, a decision will be made by the study team, after advice from the relevant authorities and the participant's IBD team, as to whether the participant should be withdrawn from either the study. However, we do not envisage a situation, except death, in which a participant would need to be withdrawn.

Arrangements will be made by the study team for further assessment and management as agreed with the relevant authorities, IBD team, GP and participant.

The investigator will provide the study team with a 1-month follow-up report on all SAEs. Further monthly reports should be provided in the absence of resolution. These reports will be communicated to the Programme Steering Committee, REC, and to the local R&D office. Blank Adverse Event Forms (Sponsor's standard form) will be distributed to sites that are recruiting.

AEs that do not require reporting: Expected AEs include planned/elective hospitalisations, or unplanned but expected hospitalisation due to flare-up of IBD: these are expected during the course of the study and will not be collected as SAEs.

Stopping rules

The study may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the Steering Committee or REC concerned. The study may also be prematurely discontinued due to lack of recruitment or on advice from the Programme Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the Sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

9.8 Intellectual property

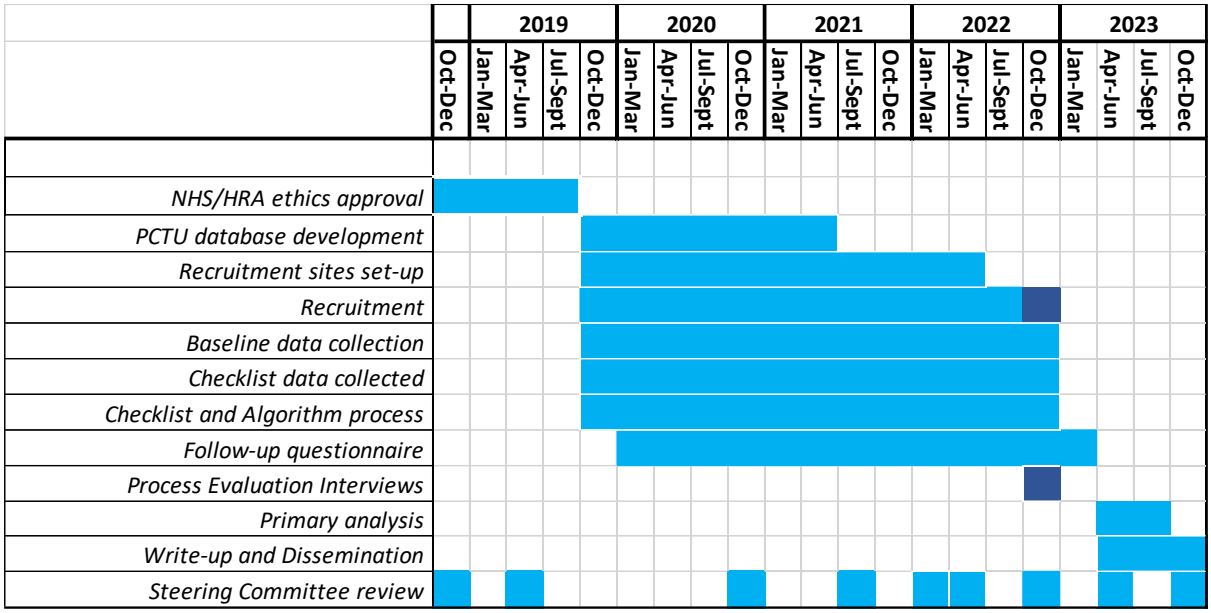
Any intellectual property arising from the development, conduct and completion of this study will be owned by the study Sponsor.

10. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the IBD-BOOST programme manager in collaboration with the CI, and through the Programme Management Group.

The Programme Management Group deliberates the practical and logistical aspects of the study, for example, agreeing local procedures for recruiting, including who will recruit, who will consent, workspace available for recruiting / consenting and how this will operate alongside standard clinic operations. The programme is overseen by a Programme Steering Committee whose members are independent of the programme and liaise with the study funders, the NIHR. In the case of study deviations or serious breaches of protocol, a study deviation form will be completed and forwarded to the Programme Steering Committee and the study Sponsor.

10.1 Study Gantt chart



11. DISSEMINATION

The Sponsor owns the data arising from the study and the CI will act as the custodian of this data on behalf of the Sponsor. On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared. The full study report can be accessed on request to the CI. The participating investigators will have rights to publish any of the study data by prior agreement with the CI and the Programme Management Group. There will be no time limits or specific review requirements on the publications.

The funding body (NIHR) will be acknowledged within the publications and review draft publications before journal submission. We do not plan for the study protocol, full study report, or anonymised participant level dataset to be made publicly available.

12. PUBLICATION POLICY

To health professionals who could develop services, and the academic community

We will submit results for publication in multidisciplinary academic journals (such as Inflammatory Bowel Diseases and Journal of Crohn's & Colitis) to disseminate to professional audiences. We will submit to key IBD conferences, including but not limited to the UK British Society of Gastroenterology, the European Crohn's & Colitis Organisation and the USA Digestive Diseases Week.

To patient groups

We will work with our patient and public volunteers, training those who are willing to present results at local and regional Crohn's & Colitis UK meetings. We will work with patients to construct a user-friendly lay summary for the CCUK newsletter and website. We will prepare a more detailed summary of results in lay language for participants and people with IBD who request this and adapt the charity information sheets on bowel control, fatigue and pain

accordingly. We will discuss dissemination via their newsletter with the European Federation of Crohn's & Colitis (patient) Associations. The study team are members of all these groups.

Authorship eligibility guidelines and any intended use of professional writers

The co-applicants and anyone else who makes a substantive contribution during data analysis or interpretation (including those involved through PPI) will be eligible to be co-authors.

The results from different centres will be analysed together and published as soon as possible. All publications will follow the guidance set out by the NIHR in 'Identity guidelines and research outputs management for principal investigators'. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Programme Management Group has published its report. The Programme Management Group will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participating centres, and if there are named authors, these should include the project's Chief Investigator. The order of the named authors should be agreed in advance and should reflect the level of input by each author.

No verbal or written report may be made without the approval of the Programme Management Group. The Sponsor should be consulted for review of any final report before it is disseminated for wider circulation or publication.

It is not intended to use any professional writers.

13. PEER REVIEW

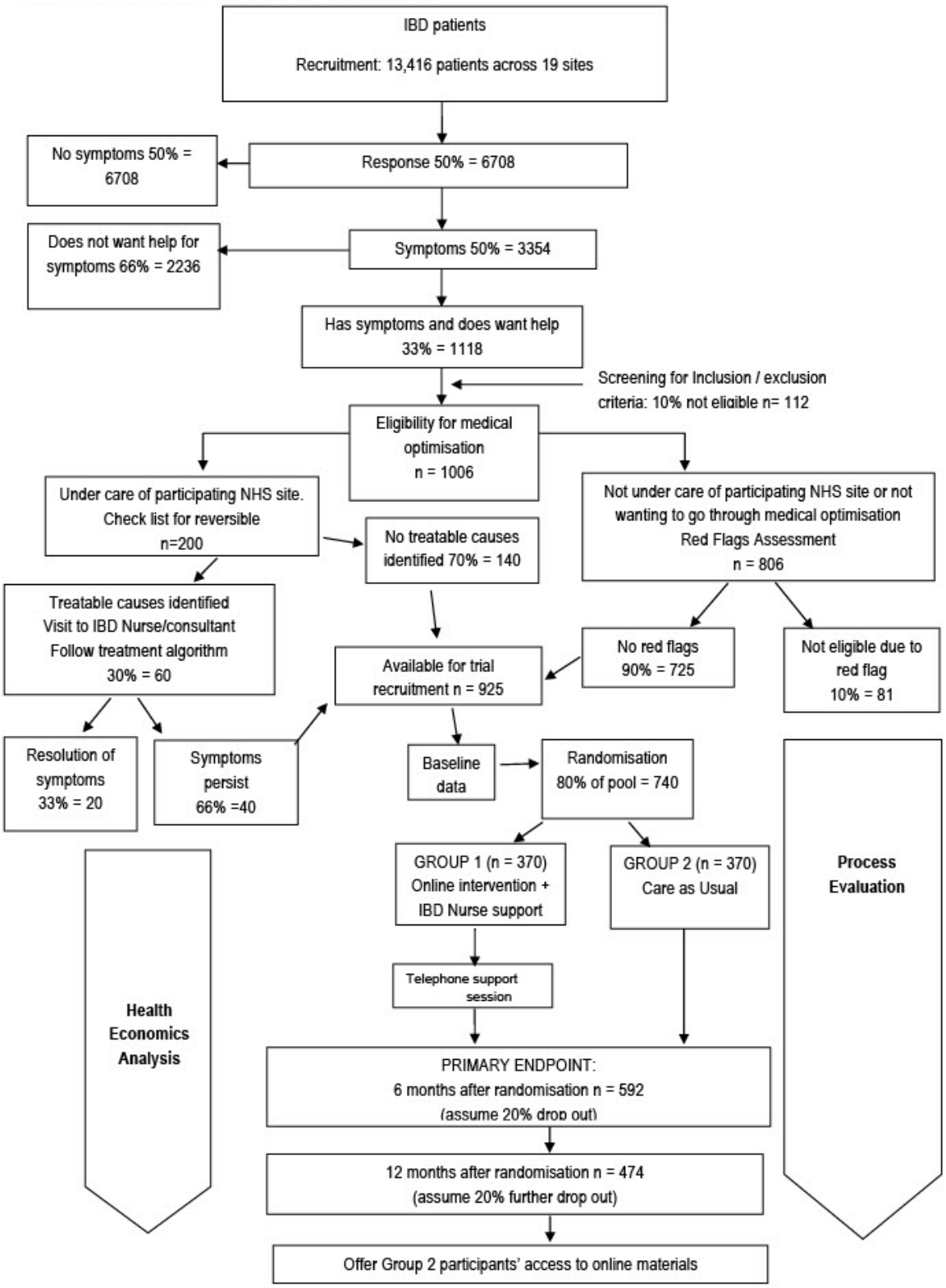
15 peer reviewers commented as part of grant funding process: 2 stage grant application with amendments made as suggested by peer reviewers.

14. PATIENT & PUBLIC INVOLVEMENT

People with IBD have been extensively involved in developing the IBD-BOOST programme. In particular PPI has informed or will inform:

- Identification of the research questions for the programme
- The content of the checklist and algorithm
- Design of the research (including development of patient-facing materials such as the questionnaires and Participant Information Sheet)
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings

Appendix 1: IBD BOOST Participant Flow Chart



Appendix 2: PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Detail the reason(s) for the protocol update
	1.0	27.02.2019	N/A
	2.0	15.04.2019	Changes following REC review.
	3.0	09.08.2019	Substantial amendment to add to paper copies.
	4.0	22.09.2020	Substantial amendment. Minor clarifications on paper copies. Updated study timelines and Gantt chart. Added Appendix 14.
	5.0	08.01.2021	Minor clarifications on storage of study documents. Updated study times and Gantt chart. Added appendix 15. Recruitment target updated.
	6.0	17.06.2021	Non-substantial amendment with updates to include detail that reminder email/texts for 3 month follow up questionnaire will be sent.
Current	7.0	16.08.2022	Substantial amendment. • Update of sponsor representative, NIHR representative and trial statistician contact details. • Update of methodology, objectives/aims and analysis to include qualitative process evaluation interviews with study staff members. • Update of recruitment duration from 40 to 43 months. • Update of research sites, and programme co-investigators, research team and programme steering committee members updated. • Update of appendices to include process evaluation interviews PIS, topic guide and consent forms.

			• Update of the IBD-BOOST programme of research. • Update of secondary research questions. • Clarification of study design and population, and update of sample size. • Update of outcome measures and corresponding references. • Update of study schedule. • Update of data management to include process evaluation interviews. • Update of Study Gantt chart. • Update of Appendix 1: IBD BOOST Participant Flow Chart. • Update of references.

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