NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

Synopsis

Management of diarrhoea in patients with stable ulcerative colitis with low FODMAP diet, amitriptyline, ondansetron or loperamide: the MODULATE RCT

Lauren A Moreau,[1*] Alexander Charles Ford,[2] Matthew James Brookes,[3] Sandra Graca,[1] Elspeth Guthrie,[4] Suzanne Hartley,[5] Lesley Houghton,[6] Karen Kemp,[7] Nicholas A Kennedy,[8] Yvonne McKenzie,[9] Delia Muir,[1] Pei Loo Ow,[1] Christopher Probert,[10] Emma Pryde,[11] Christopher Taylor,[1] Thomas A Willis,[1] Alexandra Wright-Hughes[1] and Amanda J Farrin[1]

[1]Clinical Trials Research Unit, University of Leeds, Leeds, UK
[2]Leeds Institute of Medical Research at St James's, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[3]The Royal Wolverhampton NHS Trust, Wolverhampton, UK
[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[5]NHS England, Leeds, UK
[6]Division of Gastroenterology and Surgical Sciences, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK
[7]Manchester University NHS Foundation Trust, Manchester, UK
[8]Royal Devon University Healthcare NHS Foundation Trust, UK/University of Exeter, Exeter, UK
[9]Digestible Nutrition, UK/Nuffield Health, Oxford, UK
[10]Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK
[11]Patient and Public Engagement, UK/Crohn's and Colitis UK Research Champion, Leeds, UK

[*]Corresponding author l.a.moreau@leeds.ac.uk

Published March 2025
DOI: 10.3310/GHFE4871

Abstract

Background: Many patients with ulcerative colitis report ongoing diarrhoea even when their disease is stable and in remission.

Design: MODULATE was a pragmatic, multicentre, seamless, adaptive, phase 2/3 open-label, parallel-group, multiarm multistage randomised controlled trial.

Setting and participants: People aged over 18 years with stable ulcerative colitis who had diarrhoea, recruited from secondary care sites in the United Kingdom.

Interventions: The control arm consisted of modified first-line dietary advice given to all patients with irritable bowel syndrome; the first interventional arm was amitriptyline, a tricyclic antidepressant, which at low doses slows colonic transit; the second intervention was loperamide, an antidiarrhoeal drug also thought to slow colonic transit; the third was ondansetron, an antiemetic thought to slow colonic transit; and the fourth was a diet low in fermentable oligo-, di-, and mono-saccharides and polyols, which is thought to reduce bloating and gas within the small intestine. All patients randomised to an interventional arm were to receive treatment for 6 months.

Main outcome measures: Primary outcome measures: Phase 2: Improvement in diarrhoea measured using the Gastrointestinal Symptom Rating Scale-irritable bowel syndrome questionnaire at 8 weeks post randomisation: improvement defined as those reporting minor discomfort from diarrhoea or less (scoring ≤ 2 on the diarrhoea subscale).

Secondary outcome measures: Phases 2 and 3: Measured at both 8 weeks and 6 months:

This synopsis should be referenced as follows:
Moreau LA, Ford AC, Brookes MJ, Graca S, Guthrie E, Hartley S, *et al*. Management of diarrhoea in patients with stable ulcerative colitis with low FODMAP diet, amitriptyline, ondansetron or loperamide: the MODULATE RCT [published online ahead of print March 12 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/GHFE4871

1. Improvement in diarrhoea measured using the Gastrointestinal Symptom Rating Scale-irritable bowel syndrome.
2. Blood for C-reactive protein, stool for faecal calprotectin at 6 months only, reviewing case notes for escalation of medical therapy for ulcerative colitis.
3. Anxiety and depression, via the Hospital Anxiety and Depression Scale.

Results: The MODULATE trial opened in December 2021 and closed in January 2023. Of the eight secondary care sites that completed contracting, only four opened to recruitment during this time, and one person was randomised. Trial timelines coincided with the start of the COVID-19 pandemic, causing substantial delays and, ultimately, its early closure. During this time, the trial underwent two major redesign phases, enabling a fully remote participant pathway incorporating electronic consent, remote data capture, posted blood and stool sample kits for eligibility screening, delivery of the dietary intervention via telephone or video call platform, postage of trial investigational medicinal products directly to participants' homes and all trial follow-up appointments conducted via telephone. The second phase of redesign pushed the trial towards a fully decentralised model. However, this stage was not implemented due to the decision to close the trial early.
Limitations: The study was unable to recruit the necessary sample size, preventing the trial from progressing. The trial met with several challenges. The Trial Steering Committee's root cause analysis concluded that the pandemic was the leading factor in trial closure, especially regarding our ability to recruit both sites and participants.
Conclusions: Although the trial closed early and with insufficient participants to proceed with full statistical analysis, lessons were learnt that could potentially inform future remote trial design and decentralised participant pathways.
Future work: MODULATE was a commissioned call in response to a priority question identified by people living with ulcerative colitis. The question remains important and unanswered; trials to address it are needed. Given the recruitment difficulties we experienced, consideration should be given to conducting these in both primary and secondary care.
Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 17/33/03.
A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GHFE4871.

Synopsis

Introduction

This section summarises MODULATE protocol version 7.0, 17 September 2021. The full protocol is presented in *Report Supplementary Material 1*.

This report provides an overview of the MODULATE study. The original trial was designed during 2019 for conventional, in-person delivery. In response to the COVID-19 pandemic, a hybrid protocol was devised to enable the study to be delivered remotely (subject to site requirements and participant preference). Further challenges to delivery and recruitment, arising from the pandemic, resulted in the team planning a fully decentralised pathway. The initial section of this report draws upon protocol version 7.0 (17 September 2021), which details the planned remote delivery. In *Development of remote protocol*, *Development of decentralised protocol* and *Impact and learning*, we describe the obstacles faced and the rationale for a fully decentralised study, along with the decision to close the trial and the lessons learnt.

Rationale and background

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD). The mainstays of medical management are 5-aminosalicylates, immunosuppressant drugs and biological therapies.[1–3] These are used to induce remission of UC activity and to prevent future relapse. Therapy is escalated in a stepwise manner to the level required to best control disease activity and symptoms.

However, symptoms do not always predict inflammatory activity,[4] and up to 20% of people with UC experience ongoing and troublesome diarrhoea, even when there is no objective evidence of inflammation, and their level of medical therapy is appropriate.[5] These symptoms, in the absence of inflammation, have a substantial impact on the lives of people with UC. They are associated with psychological comorbidity and have a similar detrimental impact on quality of life to that associated with symptoms confirmed to be due to ongoing inflammation.[5,6] The optimal management of ongoing diarrhoea in patients with stable UC, with no evidence of active inflammation, is unclear. Stepwise escalation of therapy may not be appropriate in this group of patients, as there are no randomised controlled trials (RCTs) to show that this strategy is effective. In addition, inappropriate use of immunosuppressant drugs and biological therapies is potentially expensive and carries a possible risk of serious side effects, like opportunistic infection or malignancy.[7–10]

An alternative approach may be to use dietary interventions and pharmacological therapies that are effective in

other conditions characterised by chronic diarrhoea, such as irritable bowel syndrome (IBS). A diet low in fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) is recommended by the National Institute for Health and Care Excellence (NICE) guidelines for IBS.[11] Drugs used in patients with IBS with diarrhoea include the antiemetic ondansetron,[12] which is a 5-hydroxytryptamine-3 receptor antagonist; low-dose tricyclic antidepressants (TCAs),[13,14] such as amitriptyline; and the antidiarrhoeal drug loperamide.[15] All these drugs can slow colonic transit.[16–18]

The evidence base for the use of any of the above treatments in patients with stable UC with diarrhoea is not strong. At the time MODULATE was designed, there had been 1 RCT of a low FODMAP diet,[19] and although this recruited patients with ongoing symptoms in the absence of inflammation, there were only 61 patients with UC included in the trial. A systematic review concluded that low-dose antidepressants may have a positive impact on the natural history of IBD,[20] but identified only one RCT, which was a small pilot study of fluoxetine in Crohn's disease.[21] The authors of the review concluded that further large trials, with an adequate duration of follow-up were required. There had been no RCTs of ondansetron or loperamide in this group of patients with UC, and patients with ongoing diarrhoea often received conflicting advice about the safety and effectiveness of the latter drug in UC, even though it is available over the counter. It was therefore unclear whether any of these treatments would lead to a benefit for patients with stable UC and ongoing diarrhoea, in terms of an improvement in symptoms and quality of life. As a result, guidelines from NICE and the British Society of Gastroenterology (BSG) made no recommendations as to how to manage this group of patients.[22,23] Although new therapies for UC continue to be developed, these are usually expensive and are only tested in patients with active mucosal inflammation.

Given that the specific mechanism of diarrhoea was unclear in this group of patients with UC, assessing multiple therapies within a single trial would maximise the efficiency of the design. The MODULATE trial aimed to help clinicians, patients and health service planners make better-informed decisions regarding the management of diarrhoea in patients with stable UC in secondary care.

Trial design

MODULATE was designed as a pragmatic, multicentre, seamless, adaptive, phase 2/3 open-label, parallel-group, multiarm multistage (MAMS) RCT to determine the clinical effectiveness of a low FODMAP diet, low-dose titrated amitriptyline, titrated ondansetron or loperamide either taken on demand or titrated, compared with standard first-line dietary advice, as a treatment for diarrhoea in patients with stable UC in secondary care.

Participants and personnel delivering the intervention were not blind to treatment allocation. Participant-reported outcome assessment was conducted at 8 weeks and 6 months using self-report methods (either postal or online, based on participant preference).

In response to the COVID-19 pandemic, the MODULATE trial offered a hybrid protocol enabling the study to be delivered remotely according to site requirements and participant preference. Please see *Development of remote protocol* and *Development of decentralised protocol* section of this report for further information on the phases of trial redesign.

Treatment regimens

Patients were randomised to receive a low FODMAP diet, titrated low-dose amitriptyline, titrated ondansetron, loperamide either taken on demand or titrated, or a control intervention of standard first-line dietary advice, all for 6 months. All drugs were self-titrated, supported by a titration guidance document and a study researcher, according to differing schedules, and depending on the individual's response to treatment and side effects.

Phase 2 to Phase 3 transition

Phase 2 evaluated the short-term effectiveness of all active interventions, each compared with control, in terms of improvement in diarrhoea, via the diarrhoea subscale of the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) at 8 weeks. A maximum of two of the interventions showing evidence of short-term effectiveness would proceed to phase 3 to evaluate longer-term effectiveness, assessed in terms of improved disease-specific quality of life, via the Inflammatory Bowel Disease Questionnaire (IBD-Q), at 6 months post randomisation (*Figure 1*). Participants recruited to phase 2 would contribute to phase 3 analysis where applicable (i.e. where allocated to the control arm or those intervention arms progressing to phase 3).

Internal pilot

An internal pilot across a minimum of 10 centres was planned to assess recruitment, treatment dropouts, adherence to the low FODMAP diet and follow-up rates using predefined progression criteria. The progression criteria included assessment of recruitment at 6 months, treatment dropout rates across all arms, adherence to the low FODMAP diet (given that if this were found to be unacceptable to, or infeasible for, patients, it would jeopardise the chances of this arm being taken forward

This synopsis should be referenced as follows:
Moreau LA, Ford AC, Brookes MJ, Graca S, Guthrie E, Hartley S, *et al*. Management of diarrhoea in patients with stable ulcerative colitis with low FODMAP diet, amitriptyline, ondansetron or loperamide: the MODULATE RCT [published online ahead of print March 12 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/GHFE4871

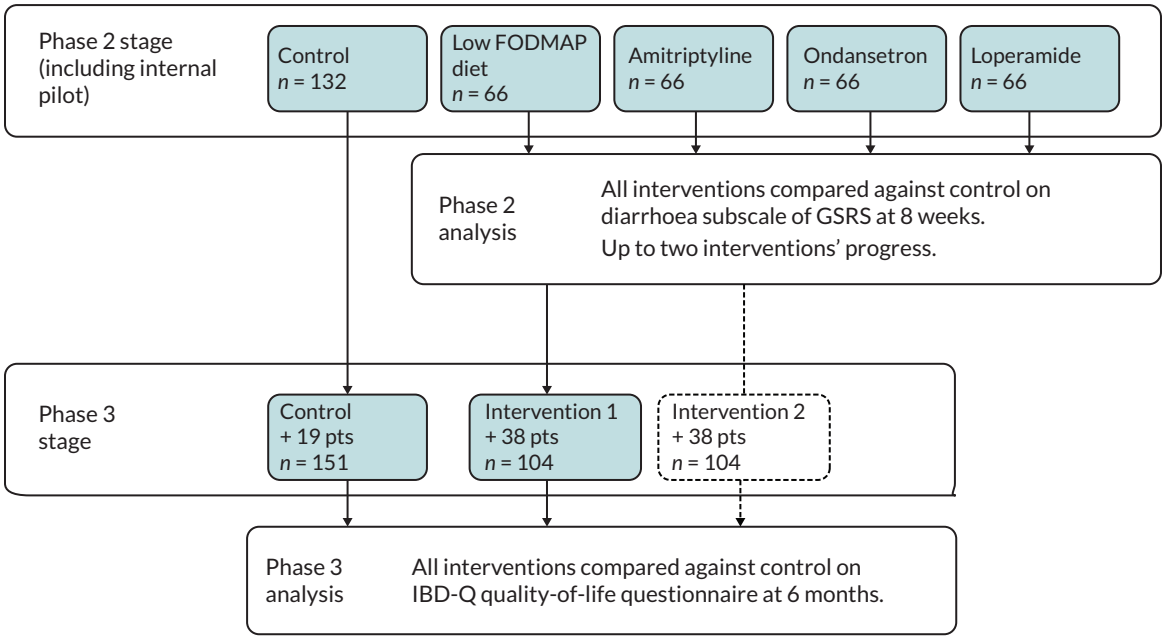

FIGURE 1 Trial design.

to phase 3) and 6-month follow-up rates all assessed at 12 months after the start of recruitment. Due to the early closure of the trial, the pilot was not assessed as planned.

Objectives and end points

Primary objectives

Our primary objectives were to answer the following questions:

1. **At phase 2:** What is the short-term effectiveness of low FODMAP diet, low-dose amitriptyline, ondansetron and loperamide, each compared with a control of standard first-line dietary advice, in terms of improvement in diarrhoea, via the diarrhoea subscale of the GSRS-IBS[24] at 8 weeks, defined as reporting minor discomfort (score ≤ 2) from diarrhoea?
2. **At phase 3:** What is the effectiveness of a maximum of two interventions continued from phase 2 (having shown evidence of short-term effectiveness) in terms of improved disease-specific quality of life, via the IBD-Q[25] at 6 months?

Secondary objectives

Our secondary objectives aimed to answer the following questions at both 8 weeks and 6 months:

1. What is the effect of the active treatments, compared with a control of standard first-line dietary advice, in terms of:
   a. improvement in discomfort from (1) loose stools, (2) diarrhoea, (3) urgency and (4) abdominal pain, each assessed via the GSRS-IBS[24]?
   b. markers of disease activity, including escalation of medical therapy, need for surgery, faecal calprotectin (FC) and C-reactive protein (CRP)?
   c. mood, via the Hospital Anxiety and Depression Scale (HADS)[26]?
2. What is the tolerability and safety of the active treatments, compared with a control of standard first-line dietary advice?
3. What is the adherence to each of the active treatments, compared with a control of standard first-line dietary advice?

Internal pilot objectives

To assess trial progression against predefined progression criteria with respect to rates of:

1. Recruitment (assessed after 6 months of recruitment);
2. Treatment dropout (assessed after 12 months of recruitment);
3. Adherence to a low FODMAP diet (assessed after 12 months of recruitment);
4. Six-month follow-up (assessed after 12 months of recruitment).

Trial methods, data collection and analysis

Trial setting

The trial planned to recruit participants from approximately 26 centres in secondary care across the UK. Potentially eligible patients could also be identified by general practitioners (GPs) in primary care and other secondary care hospitals, working as Participant Identification Centres.

Eligibility

Eligible patients were required to meet all of the inclusion criteria and none of the exclusion criteria (*Table 1*).

TABLE 1 Inclusion and exclusion criteria[a]

Inclusion criteria	1.	Age ≥ 18 years
	2.	At least moderate discomfort from diarrhoea according to the GSRS-IBS[24] (equating to a score of ≥ 4 on the diarrhoea subscale of the GSRS-IBS)
	3.	On stable doses of UC-related medication for ≥ 2 months at the time of initial screening telephone call
	4.	Ongoing diarrhoea for 3 months prior to initial screening telephone call
	5.	A CRP < 5 mg/l (measured as per local practice) within 4 weeks prior to randomisation
	6.	FC < 250 mcg/g[27] within 4 weeks prior to randomisation
	7.	Stable UC at the time of randomisation, in the clinical opinion of the gastroenterologist
	8.	No evidence of active suicidal ideation at the time of initial screening telephone call and prior to randomisation, as determined by the three clinical screening questions below: a. Whether the patient has experienced any thoughts of harming themselves, or ending their life in the last 7–10 days? b. Whether the patient currently has any thoughts of harming themselves or ending their life? c. Whether the patient has any active plans or ideas about harming themselves, or taking their life, in the near future?
	9.	No recent history of self-reported self-harm (an episode of self-harm within the last 12 months)
	10.	Willing to be considered for all treatment arms of the trial, and to remain in the treatment arm to which they are assigned
	11.	If female, must be: a. postmenopausal (no menses for 12 months without an alternative medical cause), or b. surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or c. using highly effective contraception (and must agree to continue for 7 days after the last dose of the investigational medicinal product)
	12.	Able to complete questionnaires and trial assessments
	13.	Able to provide informed consent
Exclusion criteria	1.	IBD unclassifiable or Crohn's disease
	2.	Ulcerative proctitis
	3.	Body mass index ≤ 18.5 kg/m^2
	4.	Previous or planned gastrointestinal IBD-related resectional surgery or previous cholecystectomy
	5.	Having received steroids for UC within the last 2 months prior to the initial screening telephone call or at randomisation
	6.	Coeliac disease (as confirmed via anti-tissue transglutaminase antibodies)
	7.	A previous diagnosis of colorectal dysplasia or cancer, or no up-to-date surveillance colonoscopy, as per current BSG guidelines[28]
	8.	Known allergy to TCAs, ondansetron or loperamide

continued

TABLE 1 Inclusion and exclusion criteria[a] (*continued*)

9. Current use of a TCA at the time of the initial screening telephone call or at randomisation
10. Previous failed treatment with, or regular use of, amitriptyline, ondansetron or loperamide for diarrhoea
11. Currently on, or have previously tried and failed, a low FODMAP diet under dietitian guidance
12. Contraindications to the current use of TCAs, including patients with any of the following:
    a. taking monoamine oxidase inhibitors, or receiving them within the last 2 weeks
    b. already currently prescribed a TCA for the treatment of depression
    c. previous myocardial infarction
    d. recorded arrhythmias, particularly heart block of any degree, or prolonged QT interval on electrocardiogram
    e. mania
    f. severe liver disease
    g. porphyria
    h. congestive heart failure
    i. coronary artery insufficiency
    j. receiving concomitant drugs that prolong the QT interval (e.g. amiodarone, terfenadine or sotalol)
13. Contraindications to the current use of ondansetron, including:
    a. concomitant use of apomorphine
    b. concomitant use of other drugs that prolong the QT interval
14. Contraindications to the current use of loperamide, including:
    a. acute UC
    b. acute dysentery, which is characterised by blood in stools and high fever
    c. bacterial enterocolitis caused by invasive organisms
    d. pseudomembranous colitis associated with the use of broad-spectrum antibiotics
15. Pregnancy, planned pregnancy during the study, pregnancy within 3 months of study completion or breastfeeding

a For full explanation of eligibility criteria, please see the protocol, *Report Supplementary Material 1*.

Recruitment, randomisation and blinding

See *Figure 2* for a flow diagram of participant identification and screening, and *Figure 3* for a flow diagram of participant registration and randomisation.

Participant identification

Potential patients were identified using four strategies:

1. Approached in standard secondary care clinics (including virtual clinics) about the trial by a member of the attending clinical team and provided with verbal and written details.
2. Searching existing, relevant, clinic lists and hospital databases for patients with stable UC. Those that reported diarrhoea, without objective evidence of disease activity, could be contacted by telephone, letter or e-mail to inform them about the trial, and invited to take part in an initial telephone screening call.
3. To alert existing patients to the study, we used posters and leaflets in clinic waiting areas and other appropriate locations. Information about the study was also included on relevant websites and research databases accessible by members of the public with UC who were interested in opportunities to take part in research.
4. The NIHR BioResource platform was used to alert patients in the proximity of participating centres to the study and to then self-screen using the Clinical Trials Research Unit (CTRU) MODULATE self-screening website. Patients who were identified as potentially eligible were asked to consent to sharing their details with their local participating hospital, who would make contact to arrange further screening.

Postal invitations included an invitation letter, the participant information sheet (PIS), contact details of the research team and a reply slip. Patients interested in taking part in the study were asked to return the reply slip or contact the research team directly. See *Report Supplementary Material 1* for PISs.

Telephone screening

The research nurse, or the authorised delegate at each participating centre, sought verbal consent to

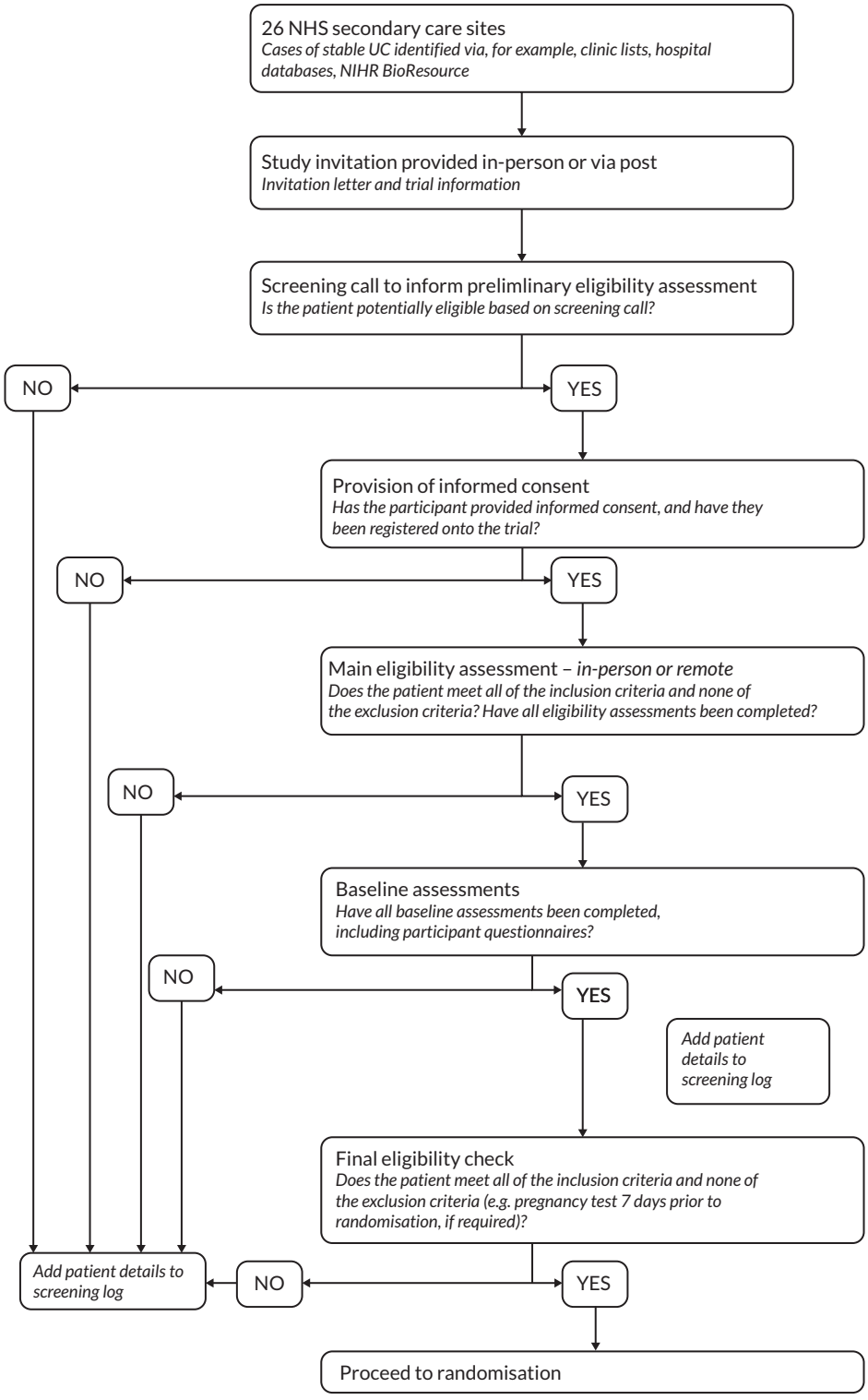

FIGURE 2 Participant identification and screening.

telephone-screen interested patients. If the participant was potentially eligible, the following options were available depending on availability of remote services, including the use of a central laboratory to dispense and analyse blood and stool sample kits, and patient preference:

1. The nurse (or the delegate) would invite the patient to attend a clinic appointment to confirm eligibility. If preferred, a stool sample kit could be sent to their home address to allow the participant to bring a stool sample to their clinic visit; or

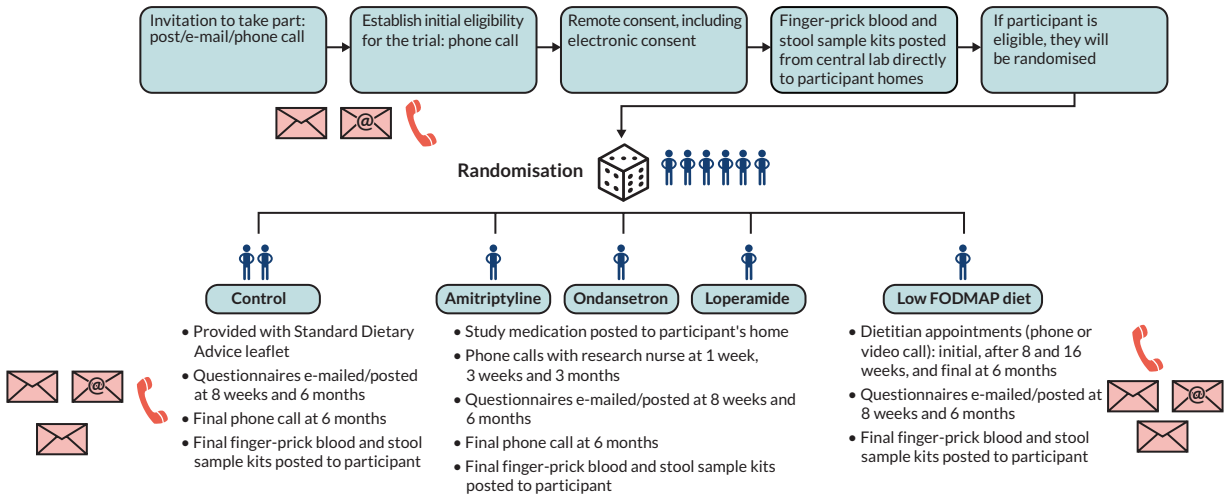

FIGURE 3 Remote trial pathway.

2. The nurse (or the delegate) would arrange for a stool and blood kit to be sent to the patient's home from a central laboratory (which was returned to the central laboratory for analysis). The results of the laboratory analysis were uploaded via a secure portal, accessible by the site. Eligibility was confirmed via a telephone appointment.

Informed consent

The local principal investigator (PI) retained the overall responsibility for the informed consent of participants at their site.

A record of informed consent was taken using either:

1. Face-to-face consent during a clinic visit.
2. Remote postal paper consent.
3. Remote electronic consent (e-consent) on an electronic database (REDCap).

Informed consent was obtained prior to the potential participant undergoing trial procedures after the telephone screen.

Participants identified as potentially eligible, after telephone screening, were asked to attend either an in-person or telephone appointment with their local research team. The investigator, or the authorised delegate, would discuss the trial in detail with the patient, providing a comprehensive overview of the study, including the background, the purpose and the risks and benefits of participation.

Patients were given as long as they needed (at least 24 hours, unless the participant wished to participate sooner) to consider participation and were given the opportunity to discuss the study with their family and healthcare professionals.

The right of a participant to refuse participation without giving reasons was respected, and participants remained free to withdraw at any time from the study, without giving reasons and without prejudicing their further treatment. Methods for processing witnessed consents and handling instances of loss of capacity were available where required.

Roles and responsibilities of inflammatory bowel disease specialist nurses

Inflammatory bowel disease nurse specialists are autonomous practitioners and have advanced knowledge and clinical skills to provide expert care and management of patients with UC. In recognition of this level of training, MODULATE extended the roles of local PI, prescription of investigational medicinal product (IMP), review of medications and informed consent to IBD nurse specialists (where training, including good clinical practice certificate, qualification and local site practice permitted).

Registration and screening assessments

Following confirmation of informed consent, patients were registered into the trial by an authorised member of staff at the local research site and underwent the following assessments to confirm eligibility:

- CRP (must be < 5 mg/l within 4 weeks prior to randomisation).
- FC (must be < 250 mcg/g within 4 weeks prior to randomisation).
- Anti-tissue transglutaminase (tTG) to exclude coeliac disease, if the patient did not have an historically negative anti-tTG result available in their medical records.

- In the case of clinical uncertainty regarding the stability of the patient's UC, patients could be required to undergo a limited flexible sigmoidoscopy to confirm mucosal remission (endoscopic Mayo score ≤ 1). (The original protocol had included a requirement for all participants to undergo a sigmoidoscopy. However, this requirement was removed as part of a subsequent protocol amendment because patients were vulnerable and shielding for much of the COVID-19 pandemic and would not be able to attend an appointment for a sigmoidoscopy to confirm eligibility.)
- Assessment of body mass index (must not be ≤ 18.5 kg/m^2 at screening).
- Negative pregnancy test for people of childbearing potential (those not postmenopausal or surgically sterile), which had to be performed within 7 days prior to randomisation.

Blood and stool samples collected remotely were sent directly to a central laboratory, Exeter Clinical Laboratory, based at the Royal Devon University Healthcare NHS Foundation Trust, for analysis, unless sites or patients preferred to analyse their samples locally, and therefore required a patient to attend a phlebotomy appointment (as per local practice) and to drop off a stool sample.

If blood and stool results, and sigmoidoscopy (if deemed necessary by the treating physician), were normal, the patient was required to complete a baseline questionnaire pack remotely and undertake a home pregnancy test posted out to the patient's home, if required, before randomisation.

If the blood or stool tests showed an abnormal result, the individual was referred back to their gastroenterologist for further assessment.

Biological samples collected from participants as part of this study were transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes, and such activities met the requirements set out in the 2004 Human Tissue Act (and any successor legislation).

Randomisation

Prior to randomisation, patients must have provided full informed consent, previously been registered onto the MODULATE trial, have been confirmed as being eligible by a medically trained doctor, and completed the baseline assessments. Randomisation was performed centrally using the CTRU 24-hour randomisation service by the research nurse, or another authorised member of the research team. Randomisation was via minimisation, incorporating a random element, stratified according to centre, degree of discomfort from diarrhoea (score ≥ 5), extent of UC (left-sided or extensive) and HADS score (HADS score ≥ 8). In phase 2, participants were randomised to one of the four active intervention arms or the control arm in the ratio 1 : 1 : 1 : 1 : 2, with the larger group receiving the control intervention. In phase 3, participants were planned to be randomised in the ratio 2 : 1 or 2 : 2 : 1, depending on the number of active interventions taken forward, with the smaller group receiving the control intervention.

Following randomisation, an automatically generated e-mail was sent to the research team and pharmacy or dietitian, depending on allocation. The research site then:

- Ensured the participant was provided with a trial identification card, which provided their treatment allocation and all trial appointment dates. The participant was informed that the card should be carried at all times and presented to medical staff should they be admitted to hospital during their time on the trial.
- Posted the relevant participant pack to the participant's home, containing all paper resources required during the trial, as well as the participant's trial identification card.
- Notified the participant's GP of their participation in the trial using the approved study GP letter.

Blinding

Participants and personnel delivering trial interventions were not blinded to treatment allocation.

Interventions

It was expected that participants would begin their trial treatment within 1 week of randomisation.

Investigational medicinal products

Participants randomised to receive amitriptyline were to be advised to commence at a low dose of 10 mg (one tablet) to be taken once daily (OD) at night. Self-led dose titration, up to a maximum of 30 mg OD at night (three tablets), could occur during the first 3 weeks of treatment, depending on side effects and response to treatment.

Participants randomised to receive ondansetron were advised to commence at an initial dose of 4 mg (one tablet) OD. If symptoms did not improve, then self-led dose titration could occur during the first 2 weeks of treatment. The dose could be increased by 4 mg (one tablet) every 2 days until a stable dose was achieved, up to a maximum dose of 8 mg three times per day (24 mg per day, or six tablets daily).

Participants randomised to receive loperamide were to be given the option to use this as required, or to commence on 4 mg per day (two capsules) and self-titrate the dose upwards to a maximum of 16 mg per day (eight capsules), depending on symptoms.

It was planned for participants to be provided with an initial 1-month supply of amitriptyline, or a 2-month supply of ondansetron or loperamide, depending on allocation. This allowed for the maximum titration of each IMP within the relevant time period.

Participants were given a dose guidance document to support self-titration of each of these drugs and received a telephone call from a researcher on day 7 to offer support, and further calls at week 3 and month 3, with treatment continuing for a total of 6 months. Please see *Report Supplementary Material 2* for the dose guidance documents for each drug.

Participants were asked to record adherence via a self-reported summary question asked at 8 weeks and 6 months. To self-monitor adherence, a patient diary was provided to participants following randomisation.

Dispensed trial IMP could be collected by the participant from the participating trial site. Alternatively, trial IMP could be posted to the participant by Royal Mail Signed For® delivery, via courier to their home address or in line with local practice for the postage of medications.

Low fermentable oligo-, di-, and mono-saccharides and polyol diet

Participants randomised into the low FODMAP diet arm of the study, it was planned to instruct them to restrict intake of fructans, galacto-oligosaccharides, polyols, lactose and fructose (in high levels, or foods in which fructose is in excess of glucose) until the end of week 8, with counselling from a specialist gastroenterology dietitian.

If participants saw an improvement in their symptoms after 8 weeks, they would have continued onto FODMAP reintroduction. After reintroduction, the dietitian could then interpret the participant's specific FODMAP triggers and work towards establishing a long-term personalised diet. This involved fully reintroducing FODMAPs that were tolerated well, and only restricting foods that triggered symptoms.

Dietitian appointments were planned for within 1 week of randomisation, at 8, 16 (telephone review) and 24 weeks either remotely, via telephone or video call platform, or at each site's usual outpatient dietetic clinic. Education, resources and support were provided to participants to help them to incorporate the low FODMAP restriction into their daily activities at home.[29–31] See *Appendix 1 Table 4*, for further detail of the low FODMAP diet delivery appointment content and adherence measurement.

Low fermentable oligo-, di-, and mono-saccharides and polyol training

Dietitians familiar with delivering the low FODMAP diet to gastroenterology patients with IBS-like symptoms were selected to deliver the intervention. Dietitians were expected to have King's College accreditation or have been suitably trained by someone who had such training.[32]

To minimise interdietitian variation and ensure fidelity, dietitians received detailed intervention training in remote training sessions. Training was delivered by the lead trial dietitian using the site's preferred video call platform. Training was limited to a single workshop, but ongoing training and support was planned to be provided as required, and documented.

To ensure that the low FODMAP dietary intervention was delivered as intended consistently across sites, fidelity was planned to be monitored using a bespoke fidelity checklist.

Control

All participants continued their usual treatment for UC during the trial and were provided with a modified version of the NICE-approved British Dietetic Association (BDA) dietary advice sheet for IBS. They were advised not to alter their diet in any other way, unless they were in the low FODMAP diet arm of the trial. See *Report Supplementary Material 3* for the dietary advice sheet (modified from the NICE-approved BDA dietary advice sheet for IBS).

Concomitant treatments

Concomitant medication reviews and confirmation that the patient was not taking any prohibited or restricted medication took place during week 1, week 3, and month 3 telephone calls. It was the responsibility of the local PI (or the delegate) to review any new concomitant medication at the study visit and confirm the patient's continuing suitability for the study.

Discontinuation of treatment and treatment after participation

In line with usual clinical care, cessation or alteration of regimens at any time was at the discretion of attending clinicians or the participants themselves. Following participation in the study, subsequent patient care was decided by the patient's consultant gastroenterologist, according to usual practice.

Trial assessments and data collection

Data were collected by remote data entry (RDE) on electronic case report forms (CRFs) managed by the CTRU at the University of Leeds. Full details of data collection methods can be found in the full MODULATE protocol, *Report Supplementary Material 1*. The schedule of assessments is detailed in *Table 2*.

Participant questionnaires

All participants were asked to complete questionnaires at baseline, 8 weeks and 6 months post randomisation. Participants were offered the option to complete questionnaires online or on paper.

Safety

Participants in all arms self-reported adverse events (AEs) on the participant questionnaires at 8 weeks and 6 months, via the confirmation of occurrence and corresponding severity (mild – noticeable, but not preventing normal activities; moderate – restricting some activities; severe – preventing any activities) of any of the following:

- constipation
- abdominal pain or bloating (as part of the condition being treated)
- headache
- nausea
- vomiting
- rectal bleeding
- dizziness
- drowsiness
- dry mouth
- insomnia.

All serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) were collected for the duration of the trial.

Adverse events of special interest

Constipation

This was collected by participant self-report on the 8-week and 6-month questionnaires.

Flare of disease activity

Any participant suspected to have a flare of disease activity was required to have immediate investigation as follows:

- Blood for CRP (normal result < 5 mg/l).
- Stool for FC (normal result < 250 mcg/g).

If the CRP and/or the FC results were abnormal (CRP ≥ 5 mg/l, FC ≥ 250 mcg/g), the patient would have a limited flexible sigmoidoscopy to assess for evidence of mucosal inflammation. If both CRP and FC were normal, it was at the treating physician's discretion, in consultation with the participant, to decide whether a limited flexible sigmoidoscopy was still required. If a flare of disease activity was confirmed after sigmoidoscopy (endoscopic Mayo score > 1), this was classed as an AE of special interest and was expedited to the CTRU for review on the flare CRF within 24 hours of the site confirming the event. The patient's trial treatment was discontinued, and they were referred back urgently to their responsible gastroenterologist for appropriate management.

Pregnancy

All pregnancies, or suspected pregnancies, in participants were subject to reporting to CTRU within 24 hours of the PI or designee becoming aware of the event using the pregnancy CRF.

Deaths

All deaths were subject to reporting and recorded on the notification of death CRF and sent to the CTRU within 5 working days of the site research team becoming aware of the death.

Self-harm or suicide

Any reported form of self-harm, or suicide, was treated as an important medical event and reported to the CTRU on a SAE form within 24 hours of the site becoming aware of the event.

Reporting

All SAEs, SARs and SUSARs were collected from the time of consent up to 7 days after the last dose of IMP. See MODULATE protocol, *Report Supplementary Material 1*, section 12 for a full safety monitoring plan.

Oversight

Trial Steering Committee

The Trial Steering Committee (TSC), with an independent chair, provided overall supervision of the trial.

Data Monitoring and Ethics Committee

The Data Monitoring and Ethics Committee (DMEC) planned to review the safety and ethics of the trial through interim data during recruitment and treatment. The DMEC planned to meet or communicate via teleconference

DOI: 10.3310/GHFE4871

TABLE 2 Schedule of assessments

Time point / Assessments	Screening: Pre-screening call	Screening: Consent visit	Screening: Screening	Baseline	Randomisation	Week 1	Week 3	Week 4	Week 8	Month 3	Week 16	Month 6	
Verbal consent and preliminary evaluation of inclusion/exclusion criteria	X												
Suicidal ideation	X			X			X[A]			X[A]			
Duration and extent of UC	X			X									
Informed consent		X											
Registration		X											
Medical history and medications			X										
tTG			X										
FC, CRP			X									X	
Flexible sigmoidoscopy			(X)										Only required if clinical uncertainty
Pregnancy test			X										
Participants routine care team details				X									For participants recruited in the fully decentralised pathway only
Confirmation of eligibility				X									
GSRS				X[1]					X[1]			X[1]	
IBD-Q				X[1]					X[1]			X[1]	
Comprehensive Nutrition Assessment Questionnaire				X[1]					X[1]			X[1,D]	
HADS				X[1]					X[1]			X[1]	
Sociodemographic details, current meds, previous or current psychiatric diagnoses				X									

Time point	Assessments	Screening: Pre-screening call	Screening: Consent visit	Screening: Screening	Baseline	Randomisation	Week 1	Week 3	Week 4	Week 8	Month 3	Week 16	Month 6	
Loperamide usage										X[1]			X[1]	Assessment not performed for loperamide group
SAE/SAR/SUSAR check										X[1,2]			X	
Concomitant medication check										X[2]			X	
Check for flare of disease activity										X			X	
Need for either escalation of medical therapy for UC or surgery										X[1,2]			X	
Contact details check				X	X		X	X	X	X	X	X	X	Changes should be reported throughout the trial
Adherence (via diary card)										X[4]			X[4]	CTIMP groups only (A, B, C)
Unused medication return													X	
Study medication replenished								X[A]			X			
Optional clinician review									X					
Dose information							X	X			X		X	
Height					X									Low FODMAP group only
Weight					X		X			X			X	
Dietitian counselling session							X[3]			X[3]		X[3]	X[3]	

CTIMP, Clinical Trial of an Investigational Medicinal Product.
1, Completed by patient; 2, Completed by nurse; 3, Completed by dietitian; 4, For patient self-monitoring, not collected by CTRU; A, Amitriptyline group; B, Ondansetron group; C, Loperamide group; D, Low FODMAP group.

This synopsis should be referenced as follows: Moreau LA, Ford AC, Brookes MJ, Graca S, Guthrie E, Hartley S, *et al.* Management of diarrhoea in patients with stable ulcerative colitis with low FODMAP diet, amitriptyline, ondansetron or loperamide: the MODULATE RCT [published online ahead of print March 12 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/GHFE4871

approximately annually, as well as reviewing unblinded safety data at least 6-monthly.

Trial Management Group

The Trial Management Group (TMG), comprising the Chief Investigator, the CTRU team and the coinvestigators, was assigned responsibility for the clinical set-up, the ongoing management and the promotion of the trial, as well as the interpretation of results.

Sample size

Phase 2

A total of 396 participants were planned to be recruited to phase 2, 66 participants per intervention arm and 132 to the control group. This provided 90% power to detect an absolute difference of 17% (50% intervention, 33% control, odds ratio > 2) in the proportion achieving improvement in discomfort from diarrhoea on the GSRS-IBS at 8 weeks,[24] with a one-sided 20% significance level, assuming a 10% lost to follow-up rate.

The 1 : 1 : 1 : 1 : 2 allocation ratio was used to maximise efficiency,[33] as recommended in trials comparing one control group to several intervention arms.

Phase 3

The sample size for phase 3 was powered at 90% to detect a 16-point difference in the IBD-Q at 6 months to assess overall clinical effectiveness, assuming a standard deviation (SD) of 32[34,35] and an extra 10% lost to follow-up. Studies have shown that a within-patient increase in IBD-Q score of between 16 and 32 points constitutes the lower and upper bounds of a clinically meaningful improvement in quality of life.[36,37] The lowest point on this range represents the minimum clinically meaningful difference in disease-specific quality of life at 6 months.

If two interventions were carried forward from phase 2, a total of 491 participants were required with two-sided 2.5% significance: an additional 38 participants per intervention arm, and a further 19 participants in the control group (subsequent allocation ratio 2 : 2 : 1, overall ratio 5 : 5 : 7 across both phases).

If only one intervention was carried forward from phase 2, a total of 426 participants were required two-sided 5% significance: an extra 20 intervention participants, and an extra 10 control participants (subsequent allocation ratio 2 : 1, overall ratio 5 : 8 across both phases).

Data analysis

Analysis was planned to take place in three stages – the internal pilot, phase 2 and phase 3 analysis. The second of these was a formal interim analysis, planned when all participants recruited to phase 2 had completed 8-week follow-up, to determine which treatments to progress to phase 3. Final analysis was planned when all phase 3 participants in the remaining treatment arms had completed 6-month follow-up. Further information of trial end points can be found in *Appendix 2*.

Analyses were to be performed on the intention-to-treat population, which included all randomised participants analysed according to the study arm to which they were randomised, irrespective of adherence to treatment.

Phase 2 analysis

Logistic regression, adjusted for stratification factors, was to be used to compare diarrhoea responder rates at 8 weeks pairwise between the control group and each of the intervention arms individually. Results were to be expressed as odds ratios, together with one-sided 80% confidence intervals and *p*-values. Intervention arms were only to be carried forward to phase 3 if the one-sided *p*-value was < 0.2. If more than two intervention arms achieved this difference, safety and adherence would also be considered to decide which two treatment arms would progress.

Phase 3 analysis

Primary end-point analysis

Linear regression, adjusted for stratification factors and baseline IBD-Q, was planned to test for pairwise differences in IBD-Q scores at 6 months between the control group and the intervention arms. Missing data were to be imputed via multiple imputation, where appropriate. Sensitivity analyses on a per-protocol population were planned to test the robustness of the results. Results were to be expressed as point estimates, together with 95% or 97.5% two-sided confidence intervals, depending on whether there were one or two intervention arms, respectively, and *p*-values.

Secondary end-point analysis

Continuous end points (IBD-Q at 8 weeks, GSRS-IBS, HADS scores, CRP and FC) were planned to be analysed in the same manner as the primary end point, adjusted for the relevant baseline score. Binary end points were to be analysed similarly in logistic regression models. Other secondary end points pertaining to disease activity and tolerability (escalation of medical therapy, need for surgery or flare of disease activity) and adherence were to be summarised descriptively.

Exploratory moderator analyses were planned to investigate if treatment effect varied by baseline

diarrhoea severity, disease extent or mood, by testing their interaction with treatment allocation. Similarly, the number of contacts or mood during follow-up was to be tested to see if this mediated patient outcomes.

Safety analysis

Descriptive statistics for all safety data were to be summarised by arm. Details on data monitoring can be found in the trial protocol, *Report Supplementary Material 1*, section 14.2.

Results summary

Trial status

MODULATE received Research Ethics Committee (REC) approval on 10 January 2020 (26 February 2020) (initial favourable option on 10 January 2020, full approval on 26 February), Medicines and Healthcare products Regulatory Agency (MHRA) approval on 9 January 2020 and Health Research Authority (HRA) approval on 26 February 2020, with the first sites due to open in March 2020. The first site was only able to open on 6 December 2021. Trial timelines coincided directly with the start of the COVID-19 pandemic, causing substantial delays and, ultimately, its early closure. The trial team encountered several severe challenges during this time, including the pause of research and long delays in site set-up timelines, capacity concerns at site and the ability to recruit participants. The MODULATE team redesigned study processes to enable delivery via a remote protocol; although the remote pathway was attractive to sites, challenges in site set-up persisted.

After careful consideration, and in discussion with the Health Technology Assessment (HTA) programme at a monitoring meeting in March 2022 and with the TSC in June 2022, the study TMG pushed MODULATE's innovation further and planned a fully decentralised pathway. The TMG had hoped the new pathway would allow for more efficient recruitment processes through bypassing the need to set up secondary care sites, thereby removing key barriers to successful study set-up.

Substantial progress on developing the pathway was made, and by December 2022, the study team were ready to submit the required amendments to the REC, MHRA and HRA to operationalise the pathway. However, due to several ongoing challenges to the delivery of the pathway, it was no longer feasible to test the decentralised pathway sufficiently before a lengthier, costed extension would have been required, and it was anticipated that there would be a substantial delay in regulatory review, due to extended review timescales at the MHRA. Reports on MHRA performance metrics cited an average of 94.67 days to review a substantial amendment for the period from August 2022 to July 2023.[38] After discussions with the TMG and our NIHR programme manager, the team reached the very difficult decision to close the trial. Our TSC was updated with the decision and provided their support for our next steps. The TSC and DMEC committees reviewed and approved our closedown plans at a meeting held on 9 March 2023. The trial met its end of study definition on 27 February 2023.

Screening and recruitment

Sites

Starting in autumn of 2019 until the autumn of 2022, 71 secondary sites were approached to take part in the MODULATE trial. All sites were invited to take part for a second time following the trial's 'relaunch' with a remote protocol. Once invited, sites were e-mailed and/or telephoned regularly to encourage engagement in study set-up. During this time, 30 sites did not respond to the invitation at all, 14 sites declined and 27 expressed an interest. Of those that expressed interest, 13 sites reviewed the local information pack. Eight of these sites completed contracting, but only four had opened by the time of trial closure. One site closed very shortly after opening due to a lack of capacity in the research team.

Participants

Between 6 December 2021 and 27 January 2023, a total of 17 potentially eligible patients were identified. A screening call took place for eight of these patients, two patients were registered and one patient was randomised (*Figure 4*). Most screened patients were identified via secondary care (14, 82.4% across 2 sites) and three (17.6%) via the self-referral website. Self-referral invitation responses were received via BioResource, Crohn's and Colitis UK (CCUK), and the MODULATE website.

The mean age of total screened patients was 44.1 years (SD 12.7), 12 (70.6%) were female and 15 (88.2%) were white people.

Discussion/interpretation

COVID-19

The COVID-19 pandemic had a substantial impact on the MODULATE study. The trial was projected to open in March 2020, but the first lockdown in March 2020 halted all non-COVID research, preventing recruitment commencing. In addition, the specific group of patients that this study intended to treat, many of whom were taking immunosuppressant drugs, were instructed to

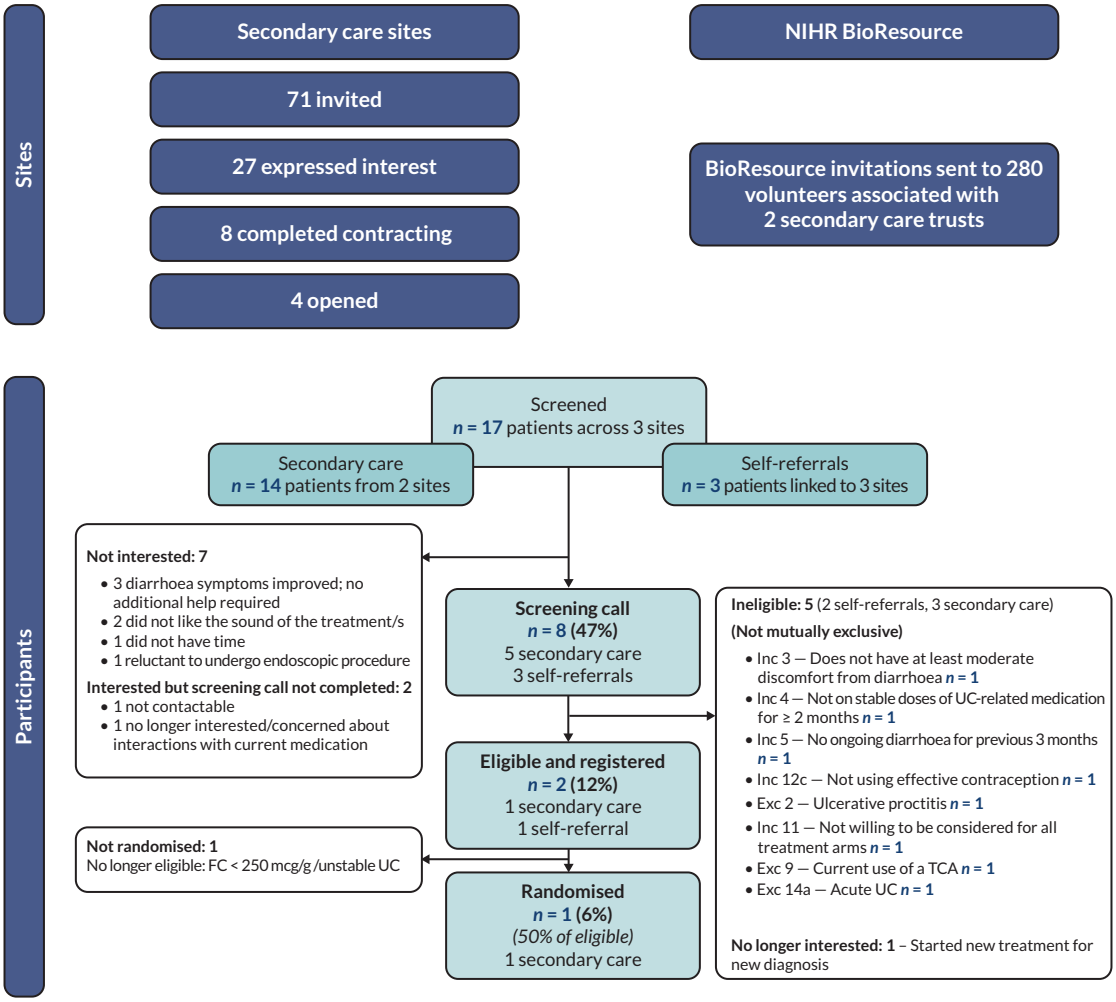

FIGURE 4 MODULATE site and participant flow diagram.

shield and would have been unable to attend hospital appointments as part of the trial.

With the release of the NIHR Restart Framework in May 2022, MODULATE was categorised as a Tier 3 study, which in practical terms led to the de-prioritisation of the study set-up across all NHS sites. Most sites were unable to continue set-up due to the lack of capacity in Research and Innovation (R&I) departments because of the focus on COVID-19 studies and urgent public health studies. Continued complications with R&I set-up continued beyond 2020 and into 2022.

Following the pause to the trial in March 2020, the MODULATE team responded proactively to the challenges presented during this period and launched a fully remote trial protocol, which was approved by the REC and the MHRA in August 2021. This included the implementation of electronic consent, postal finger-prick blood samples, postal stool samples, remote delivery of all the trial interventions, RDE and telephone study visits.

Substantial time and resources were required to set up the remote protocol. The trial team spent the period between March 2020 and August 2021 developing the REDCap e-consent system, the first of its kind used at Leeds Clinical Trials Research Unit, identifying a central lab and contracting for services, redesigning data collection systems for RDE system that was accessible by site teams, redeveloping all site training (including intervention training) to allow for remote delivery of training, and incorporating the new protocol. All participant-facing documentation was rewritten to incorporate the new participant procedures. All these alterations to the trial constituted the submission of a substantial amendment to both the REC and MHRA.

Although these innovations increased interest from secondary care centres, the capacity in R&I departments and clinical teams continued to be a barrier to successful trial set-up. Seventy-one NHS trusts were invited to set up MODULATE. However, only a total of eight sites had completed contracting by the beginning of

December 2022. The study required involvement from several departments in overstretched services, including pharmacy, IBD clinics and dietetic services. The pandemic and its effects on day-to-day services enhanced the complexity of study set-up, leading to lengthy delays and complications for teams' capacity. We opened our first trial site on 6 December 2021. By the time of closure in December 2022, we had opened only four centres in total; however, as mentioned earlier, one of these closed early due to R&I capacity issues. A further four sites were poised to open when the decision to close the trial was taken. Of the sites that opened, capacity within the IBD teams to support identification of potential participants could have contributed to low numbers of patients screened. IBD clinics, comprised clinically vulnerable patients, may have been underserved by research during this time.

Development of remote protocol

In the early months of the pandemic while non-COVID-19 research was paused, the trial team modified aspects of the trial to optimise its delivery. The trial team scrutinised the eligibility criteria, removing the requirement of flexible sigmoidoscopy for all patients. This was only required going forward if there was clinical uncertainty regarding stability of the patient's UC and at the discretion of the treating physician, reducing patient and site burden, and trial costs. The team also amended the protocol removing the requirement for patients with a historically negative anti-tTG result to undergo this assessment again.

Over the second half of 2020 and the first half of 2021, further modifications were made that ultimately allowed for the trial to be delivered on an entirely remote basis. To operationalise the remote protocol, the team sought approval for remote delivery of interventions, including postage of trial IMPs and the delivery of the low FODMAP intervention via video call or telephone. All study appointments were offered remotely via telephone call. The team contracted a central laboratory to post out kits for stool samples and finger-prick blood samples to participants to do home testing as part of trial screening. This removed the need for patients to attend outpatient appointments for hospital-based eligibility assessments. All the features of the remote protocol were underpinned using a remote consent process, including a REDCap e-consent system. E-consent processes in Clinical Trial of an Investigational Medicinal Product trials were relatively new to UK trials at this time, and this remote protocol was able to offer welcome innovation during a difficult time in secondary care research.

Plans included NIHR BioResource sending study invitations to potentially eligible patients associated with participating sites. The patients were invited to self-screen via the MODULATE website and select their local hospital to which their details would be passed. A researcher could then contact them for further screening. This opened another promising route to identify and recruit potential participants. CTRU also amended the trial systems to enable RDE at site, in the hope of improving the efficiency of trial data collection and further reduce the burden of excess paper-based data collection.

The fully remote protocol was approved by the REC/MHRA/HRA in August of 2021, allowing the first sites to open on the remote protocol. The remote protocol also allowed for 'remote' activities to take place face to face to maximise flexibility in participation from both the site and participant perspective.

The trial team believed that the remote innovations would make the trial of greater interest to potential participating sites and worked with sites throughout the autumn of 2021 to autumn 2022 to open the trial. Site set-up timelines continued to pose significant challenges and delays with several sites citing capacity concerns from both clinical and R&I perspectives. The first site opened on 6 December 2021, recruiting the first trial participant in June 2022. The second site opened on 5 January 2022 but closed on 14 February 2022 due to capacity issues. Two further centres opened on 5 April 2022 and 17 November 2022 but were unable to recruit any participants. Despite several avenues to identify and screen potential participants, few were identified in secondary care sites, and uptake on study invitations from NIHR BioResource remained low throughout the period the trial was open.

Development of decentralised protocol

In spring 2022, challenges of site and participant recruitment continued to mount; the study team once more redesigned the trial with further innovations. A new decentralised pathway was planned, utilising efficient recruitment processes; BioResource volunteers could be contacted on a national scale, without the requirement for affiliation with an open site. We had planned to work with a central research team to recruit and follow up patients. In bypassing the need to set up secondary care sites, key barriers to successful study set-up would then be removed. The team secured a central pharmacy to dispense IMP nationally and a central team of dietitians to deliver the low FODMAP diet intervention, for whom contracting was underway at the time of trial closure. A flow diagram of the proposed pathway is provided in *Figure 5*. *Table 3*, comparing the different protocol processes, is below.

Throughout summer and autumn 2022, extensive processes were outlined to support these new ways of

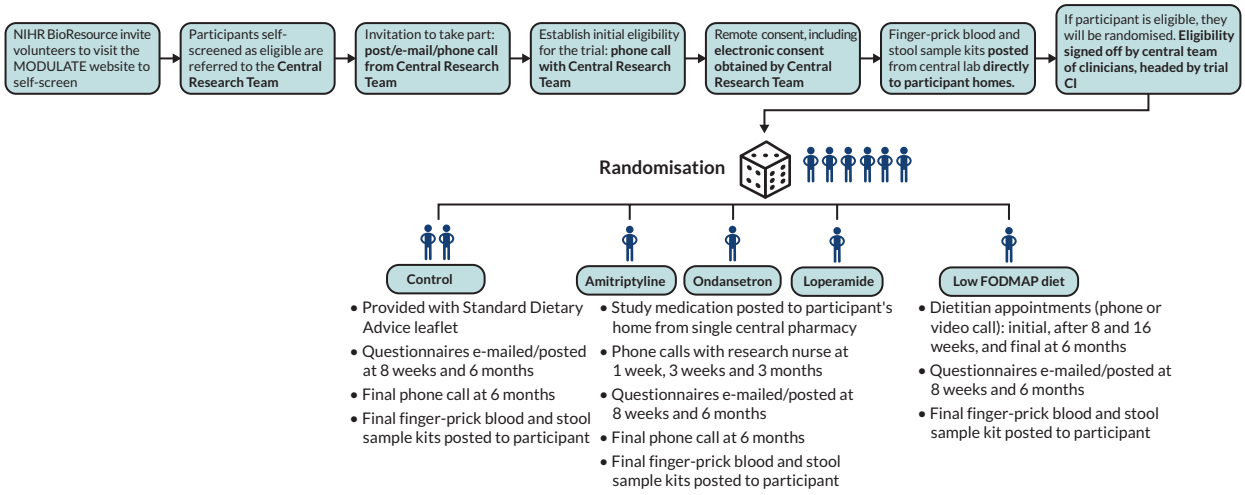

FIGURE 5 Planned decentralised pathway.

TABLE 3 Protocol processes

Trial process	MODULATE original planned protocol	MODULATE remote protocol	MODULATE decentralised protocol (not implemented)
Participant approach	In-person, in clinic	Postal approach via clinic lists, IBD registries, websites, social media	Postal approach via clinic lists, IBD registries, websites, social media
Participant consent	Paper-based	Remote (postal or e-consent)	Remote (postal or e-consent)
Eligibility assessments	In-person sample collection	Remotely collected (posted) finger-prick blood and stool samples using central lab	Remotely collected (posted) finger-prick blood and stool samples using central lab
IMP provision	In-person	Posted IMP from site pharmacy	Posted IMP from site and central pharmacy
Low FODMAP intervention delivery	Face-to-face appointment by site dietetic department	Telephone/video call intervention delivery by site dietetic department	Telephone/video call intervention delivery by site dietetic department and a central bank of dietitians employed by sponsor organisation
Trial follow-up appointments	In-person, in-clinic, telephone	Telephone	Telephone
Safety reporting	Site teams/local PI	Site teams/local PI	Central team of clinicians with referral process to usual care team

working, including new participant-facing documentation, safety escalation processes, and thorough considerations on the recording and storage of source data. The processes required to support this decentralisation were ready to submit to the REC and MHRA just prior to trial closure. NIHR HTA granted a 6-month no-cost variation to contract to enable testing of the fully decentralised pathway and evaluation of progress using predefined progression criteria. However, this was with the understanding that the team would be able to return a large proportion of funding should the new pathway prove unfeasible.

The time and work required to set up the novel ways of working were substantial and represented significant diversion from established processes previously delivered by the CTRU and sponsor organisation. Amendment paperwork was submitted to the sponsor for approval in October 2022, and although the amendment was approved for submission by the sponsor to submit to the regulators in December 2022, there were anticipated delays in regulatory review of the amendment during this period by the MHRA, which would have further jeopardised the feasibility of implementing the pathway before February or March 2023. Furthermore, the central research team, whom we had hoped would undertake the decentralised recruitment and follow-up, was unable to provide the support envisaged initially. Therefore, due to all these issues, there was insufficient time to test the pathway before a lengthier, costed extension would have been required, and the decision to close the trial was made in consultation with the TMG, the TSC and the funder.

Root cause analysis was performed in March 2023 by the TSC. The strongest detrimental factor to the delivery of the trial was identified as the COVID-19 pandemic. The pandemic caused significant delays to trial set-up including its ability to recruit secondary care sites, obtain R&I approvals in a timely manner and, in turn, participants from the sites. Ongoing changes in clinical practice, due to the pandemic, meant that the patient population for the trial were seen less frequently, and these appointments were less likely to be conducted in-person, further limiting opportunities to approach potentially eligible participants. Discussions with the trial TSC and DMEC have supported the assertion that the pandemic was the leading contributing factor to early closure of the trial.

Strengths and weaknesses of the MODULATE trial

Strengths of the MODULATE trial include:

- A platform MAMS trial with seamless phase 2/3 transition, which was designed for potential efficiency.
- Clinically relevant question, with interventions targeting an underserved patient group where no standard care pathway exists.
- Remote protocol allowing for maximum flexibility in delivery of the trial.
- The design of the trial, if delivered as intended, would have provided important results for clinicians, patients and health service planners to enable them to make better-informed decisions regarding management of diarrhoea in patients with stable UC in secondary care.

Weaknesses of the MODULATE trial include:

- Several different mechanisms for identifying participants were in place. However, screening and recruitment rates were extremely low, highlighting the need for further work into engaging with the target population.
- Further staging of participant information could have helped ensure that potential participants were in receipt of the relevant information at the right time, informing them appropriately at each step of the decision-making process. A shorter information sheet and consent form could have been provided prior to registration and eligibility assessments. Following confirmation of eligibility, the full information on trial drugs and side effects could then have been provided prior to randomisation. Streamlining and focusing information in this way may have made the trial more accessible for participants.
- Drawing parallels between diarrhoea in IBS and UC as a means of providing a rationale for the selection of the treatments used in MODULATE may have been confusing or off-putting for potential participants. Future trials in this area should, perhaps, avoid using IBS as a rationale for treatment selection.
- Set-up of platform studies can be complex for NHS sites that may be struggling with the aftermath of the pandemic and capacity to deliver research. These challenges have highlighted the need for better infrastructure and simpler information to aid in the efficient set-up of complex trials.
- MODULATE went through two significant redesign stages that offered more choice for hospitals and participants, but also added complexity to the trial.
- The self-screen website was initially designed as one of several routes to identify potential participants. The system itself was limited due to constraints at the time it was designed; only those identified as potentially eligible and consenting to data sharing were presented in trial reporting. In future studies, alternate routes of identification of participants should have fuller infrastructure built into the system, including ways to track those potential participants who are ineligible. The website also asked participants to identify their local hospital from a list of participating sites. For those potential participants who were interested, but whose local hospital was not participating, the process may have felt frustrating. In future, we would recommend including a way of keeping these potential participants informed of study progress and when a site might be open in their area.

From the point of initial pause in March 2020 until the decision to close in December 2022, the MODULATE Trial team worked continuously through two innovative redesign phases to try and deliver the trial successfully. Unfortunately, the ongoing challenges outlined above meant the trial was no longer deliverable without significant additional time and funding. MODULATE was unable to deliver on its original aims. However, both the remote protocol and planned decentralised protocol could represent significant advances in approaches to research delivery. Although not implemented, the lessons learnt from redesigning MODULATE, and its proposals for new ways of working across the NHS secondary care landscape, might inform and influence the design of efficient decentralised and remote trials in future.

Patient and Public Involvement

Our approach

Patient and public involvement (PPI) was integral to the MODULATE trial. In this section, we detail the different ways this contributed to the development and progression of the trial.

The research team invited a public contributor, with lived experiences of UC, to join the team as a co-applicant during the initial grant application, contributing to the design considerations and development of the project's lay summary. From then on, she attended all TMG meetings, contributing to decisions about patient-centred trial design.

The public co-applicant was involved in frequent communications (e-mail, face-to-face meetings and virtual meetings), contributing to all aspects of the study. For example:

- Developing the study protocols.
- Contributing to or reviewing, participant documentation. PPI input was integrated into the study documents, including, but not limited to, PISs and assessment questionnaires, web pages, video script, advertisement posters and recruitment flyers.
- Working through ethical considerations, including attending the REC review meeting along with the Chief Investigator and the trial manager and answering many questions from the committee directly.
- User testing self-screening processes – the public co-applicant took the self-screening test on the MODULATE website and completed the online questionnaire for the low FODMAP diet, to test whether the questions made sense and whether the technology worked.
- Facilitating relationships with other UC patients and a key charity partner.
- Coauthorship of this report.

Patient and public involvement support was initially provided by CTRU's PPI lead, who met with the public co-applicant to introduce PPI and discuss ongoing support needs. The PPI lead attended early meetings, before handing over PPI facilitation and support to the trial manger and CI.

In addition to input from our public co-applicant, we also met with a group of UC patients during trial set-up, who provided insights into recruitment and study design, and reviewed participant information. We initially planned to meet regularly with that group, but that was not possible due to COVID-19 restrictions. However, the public co-applicant did seek the perspective of other patients remotely at key points throughout the study.

Impact of patient and public involvement

Patient and public involvement input suggested that a MAMS design would be preferable so that patients would know exactly which individual treatments might or might not work and so be better informed when making decisions about their treatment options. This informed the basis of the design for MODULATE.

Our public co-applicant raised concerns around potential difficulties among patients with IBD in terms of willingness to consider treatments that have been used to treat IBS with diarrhoea and making everyone aware of the great sensitivity about this within the IBD patient community. This is because many patients with IBD have had the experience of their IBD symptoms being dismissed as 'just' IBS at some point prior to their diagnosis. The PPI representative went to great lengths to try to use careful language in all patient-facing documents and media, to explain the rationale for using treatments that are used in IBS with diarrhoea for ongoing diarrhoea in IBD, and to offer reassurance that the proposed use of these treatments was not in any way dismissive of the seriousness of IBD or the distress caused by ongoing symptoms.

Another concern was how willing a participant might be to have a sigmoidoscopy as part of their original eligibility assessment. Patients with IBD undergo regular endoscopies and they can be painful and distressing when there are ongoing bowel symptoms, so there may have been an unwillingness to go through yet another endoscopic procedure as part of a trial. In fact, as mentioned earlier, the need for every patient to have a sigmoidoscopy was removed because of the COVID-19 pandemic, so this issue largely resolved itself.

Other areas the public co-applicant identified as obstacles to participants taking part was a possible reluctance to have to attend extra hospital appointments due to the time and cost of attending. Therefore, every effort was made to bring patients to the hospital only when necessary and the trial was able to open on a fully remote protocol. The potential extra financial costs of buying certain foods for the low FODMAP diet were also raised, and it was decided that a voucher would be given to those participants allocated to the low FODMAP arm as compensation. Public contributors also sought reassurance that clear systems were in place and communicated to participants for what they should do in the event of a flare of their IBD during the trial.

Through the public co-applicant, contact was also made with other IBD patients to obtain feedback about how much information to give to potential participants at the initial recruitment stages, to make sure they were

informed sufficiently regarding all possible treatment arms to which they could be allocated, prior to providing informed consent.

The public co-applicant also connected the trial with the charity CCUK, with which she was already volunteering. She applied for the post of Research Champion for CCUK and was accepted. She was helped by members of the CCUK research team, who were very supportive of the trial and promoted MODULATE on their own website and developed strategies to assist with recruitment that would be used once sites started to open.

The sudden onset of the COVID-19 pandemic posed enormous challenges to the trial. Through engagement with online patient forums, the public co-applicant learnt that many patients in the IBD community were now classed as clinically vulnerable and were told to avoid mixing indoors, if possible, so were very reluctant to attend hospital appointments unless absolutely necessary. The idea of trying to deliver the trial remotely, therefore, became an important avenue to explore.

The public co-applicant also spotted a potential problem with the use of the BDA 'Standard Dietary Advice' leaflet that was to be given out to all participants in the control arm of the trial. The leaflet had been designed for patients with IBS and there were several issues with it that were inappropriate for IBD patients, including mention of 'ruling out a diagnosis of IBD' and advice that patients could seek out their own private dietitian consultation, which if participants in the control arm had done would have potentially confounded the trial results. Alterations were made to the document to make sure these issues would be communicated clearly to participants and that they would be warned which sections to ignore. These were approved for use by the BDA. This was an incredibly important change that would not have come to light without PPI review.

In addition, the public co-applicant pointed out that if the trial was fully remote and all adverts for recruitment were signposting participants to the MODULATE website, then the website had effectively become the primary recruitment gateway for the trial. However, the website had not been designed for this function and was not sufficiently easy to use for this purpose. The PPI representative therefore contacted other patients in CCUK. She therefore contacted other patients in CCUK and asked them to visit the website and provide feedback. Suggestions for how to improve the website were then fed back to the MODULATE TMG.

Once the trial had to close, the public co-applicant helped to design a clear, sensitive letter that was sent to the single recruited participant to explain what had happened.

The public co-applicant on the team has been involved in the production of this final report to HTA. She plans to use her connections with CCUK to find routes to disseminate information to IBD patients.

Learning

Despite the difficult context of COVID-19 and early trial closure, our public co-applicant was a vital team member and PPI had a big impact on the study. This project highlights the importance of building strong relationships between public contributors and the wider team, enabling effective PPI. Our public co-applicant was assured ahead of their first TMG meeting that it was ok to ask any questions of the TMG, especially if they did not understand something, for example any abbreviations used. The Chief Investigator also made sure the public co-applicant was asked their opinion directly on relevant matters at every TMG meeting. This helped to establish the ethos that the 'voice' of the patient representative was heard and respected by the TMG. This in turn gave the public co-applicant the confidence to speak up with any concerns and ask any relevant questions. The trial manager also regularly asked the public co-applicant directly for their views on a wide range of PPI issues between meetings. Thus, a mutual respectful relationship was built up between the TMG members and the public co-applicant which enabled PPI to work effectively in this trial. Early trial closure is challenging for all team members. It's important to support public contributors through that process. Our public co-applicant has joined the CTRU patient and public involvement and engagement working group, to share her experiences and help develop resources for other teams. For example, tips for contributing to TMGs and PPI considerations when closing a trial.

Equality, diversity and inclusion

MODULATE, after its initial redesign phase, offered a remote participant pathway that was able to maximise participant choice by offering both in-person and remote options for trial eligibility assessments, consent and trial interventions. The remote pathway may have been more accessible to potential participants who were not geographically close to their routine care hospital. The remote pathway would also have supported participation by members of the target population who were advised to shield in the early stages of the pandemic. Remote delivery of the trial, therefore, supported the participation of some harder to reach groups.

Patient and public involvement involvement was integrated throughout the trial's life, ensuring that trial materials were appropriately worded, alongside PPI assessment of the acceptability of the trial pathway and treatments.

Due to early closure of the trial and challenges with recruitment, we are unable to describe the characteristics of recruited participants.

Impact and learning

The trial did not complete and was unable to report on its original aims. However, the key impact and learning from MODULATE informs the need to conduct more remote and decentralised trials and the need for better research infrastructure to support the delivery of this type of research. The trial team's significant learning on delivery of remote and decentralised trials could potentially inform future projects and trial designs.

The trial team worked proactively towards redesigning the trial in two distinct phases; the need for this was dictated by the difficulties in opening the trial during a pandemic. The redesigns of the pathway required substantial staffing resources. Lessons learnt during this trial include the need for building more resilience into initial pathway design to help avoid the need for redesigning to this extent during a trial. The design work had a notable impact on the delivery of the trial including database design and data collection, requirements for contracting with new complex partner organisations, and important changes to participant procedures with implications for all participant-facing documentation. Learning from the modifications to MODULATE will enable the trial team to build in more of these flexible processes from the outset in any future research.

MODULATE has also shown that despite the trial being designed to address a priority area for the James Lind Alliance,[39] it met with challenges in reaching and engaging with the target patient population. It is likely much of this related to the COVID-19 pandemic. However, multiple, well-defined recruitment strategies are needed for any large-scale trial. MODULATE has highlighted the need for further work with registry-based recruitment and self-referral pathways that have greater capabilities and flexibility. Participant populations that may not be regularly seen face to face in secondary care sites may be challenging to reach, especially in the post-COVID clinical landscape, and investigators in this area will need to deploy several strategies to ensure research is accessible to these patients.

Implications for practice/decision-makers

As the trial did not recruit to target and was closed early, the implications for practice or for decision-makers are extremely limited, other than those already discussed. There is no impact on future management guidelines for UC arising from MODULATE.

Research recommendations

MODULATE was designed in response to a commissioned call from NIHR HTA (HTA17/33). This commissioned call asked which intervention strategy was most effective, and most acceptable to patients, in the treatment of diarrhoea associated with stable UC. It was advertised in response to a priority question identified by people living with UC in a James Lind Alliance priority setting partnership. Given the fact that the question has not been able to be addressed by MODULATE, and remains important, there is still a need for trials to examine the effectiveness of management strategies for diarrhoea in patients with stable UC. These patients may be less likely to be under regular face-to-face follow-up in secondary care, so consideration be given to conducting any future trial in both primary and secondary care.

Conclusions

The MODULATE trial closed early and with one participant randomised, there were insufficient numbers of participants to proceed with full statistical analysis. However, much experience was gained and lessons were learnt that could potentially inform future remote trial design and decentralised participant pathways.

Additional information

Acknowledgements

Trial Steering Committee and Data Monitoring and Ethics Committee

TSC: Professor Jack Satsangi, TSC Chair (University of Oxford), Dr Shanika DeSilva (The Dudley Group NHS Foundation Trust), Dr Claire Amos (MRC Clinical Trials Unit, University College London), Professor Jon Rhodes (University of Liverpool), Professor Kevin Whelan (King's College London), Dr Philip Pallman (Centre for Trials Research, Cardiff University), Emma Greenwood (PPI Representative).

DMEC: Professor John McLaughlin, DMEC Chair (University of Manchester), Professor David Rampton (Queen Mary University London), Dr Babak Choodari-Oskooei (MRC Clinical Trials Unit, University College London).

Leeds Institute of Clinical Trials Research and the University of Leeds

Thomas Morris, Florence Day, William Cragg, Kathryn McMahon, Catherine Fernandez, Steve Wilds, Adam Barratt, Amy West, Aimee Christodoulou, Gina Bianco and Maggie Barrett.

Participating centres and research collaborators

Thank you to Catherine Stansfield for key contributions throughout the development and implementation of the trial. Acknowledgements to our participating organisations, Royal Devon University Healthcare NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, Royal Wolverhampton NHS Trust, Sherwood Forest Hospitals NHS Foundation Trust.

With thanks to our research collaborators at NIHR BioResource and Exeter Clinical Laboratory.

Contributions of authors

Lauren A Moreau (https://orcid.org/0000-0002-0280-6345) (Senior Trial Manager) led on the draft of the manuscript, contributed to the remote trial protocol development, the trial's implementation and co-ordination of the data acquisition.

Alexander Charles Ford (https://orcid.org/0000-0001-6371-4359) (Professor of Gastroenterology and Honorary Consultant Gastroenterologist) conceived and designed the MODULATE trial and had overall responsibility in his role as Cochief Investigator.

Matthew James Brookes (https://orcid.org/0000-0002-8782-0292) (Professor of Gastroenterology and Clinical Consultant Gastroenterologist) contributed to the design of the trial and its implementation.

Sandra Graca (https://orcid.org/0009-0005-7299-7967) (Trial Coordinator) contributed to the implementation of the trial and coordination of trial data collection and cleaning.

Elspeth Guthrie (https://orcid.org/0000-0002-5834-6616) (Professor of Psychological Medicine) contributed to the design of the trial and its implementation.

Suzanne Hartley (https://orcid.org/0000-0003-2346-9461) (Head of Trial Management) was responsible for development of the protocol and the operational delivery of the trial.

Lesley Houghton (https://orcid.org/0000-0002-5351-0229) (Professor of Neurogastroenterology) contributed to the design of the trial and its implementation.

Karen Kemp (https://orcid.org/0000-0002-4528-6319) (Consultant Nurse in Inflammatory Bowel Disease) contributed to the design of the trial and its implementation.

Nicholas A Kennedy (https://orcid.org/0000-0003-4368-1961) (Consultant Gastroenterologist and Honorary Senior Clinical Lecturer) contributed to the design of the trial and its implementation.

Yvonne McKenzie (https://orcid.org/0000-0002-6981-9183) (Specialist Dietitian) contributed to the design of the trial, its implementation, and was the delivery lead for the low FODMAP diet intervention.

Delia Muir (https://orcid.org/0000-0003-1136-3416) (Involvement and Engagement Fellow) provided PPI advice to inform the design and trial reporting.

Pei Loo Ow (https://orcid.org/0000-0001-6025-6372) (Medical Statistician) provided statistical input into the implementation and statistical analysis plan, under the supervision of Alexandra Wright-Hughes and Amanda J Farrin.

Christopher Probert (https://orcid.org/0000-0003-4550-0239) (Professor of Gastroenterology) contributed to the design of the trial and its implementation.

Emma Pryde (PPI contributor) was responsible for providing PPI input in the design, implementation and trial reporting.

Christopher Taylor (https://orcid.org/0009-0009-8220-4923) (Senior Data Manager) provided data management input into the design and was responsible for the co-ordination of data acquisition.

Thomas A Willis (https://orcid.org/0000-0002-0252-9923) (Head of Trial Management) was responsible for operational delivery of the trial.

Alexandra Wright-Hughes (https://orcid.org/0000-0001-8839-6756) (Principal Statistician) provided statistical input into the implementation and statistical analysis plan, under the supervision of Amanda J Farrin.

Amanda J Farrin (https://orcid.org/0000-0002-2876-0584) (Professor of Clinical Trials and Evaluation of Complex Interventions and Director of Complex Interventions Division) conceived and designed the MODULATE trial, was responsible for its overall implementation across Leeds Clinical Trials Research Unit, supervised the statistical analysis and is data guarantor.

All authors reviewed and approved the final manuscript.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GHFE4871.

Primary conflicts of interest: Nicholas A Kennedy receives grants from AbbVie, Biogen, Celgene, Celltrion, Galapagos, MSD, Napp,

Pfizer, Pharmacosmos, Roche, and Takeda. He also receives consulting fees and honoraria from Amgen, Bristol Myers Squib, Celltrion, Falk, Galapagos, Janssen, Pfizer, Pharmacosmos, Takeda, and Tillotts. He also serves on the Data Monitoring Committee for the BEACON Study and is the Chair of the British Society of Gastroenterology IBD Clinical Research Group. Karen Kemp receives consulting fees and honoraria from AbbVie, Takeda, Galapagos, Dr Falk, and Lily. Alexandra Wright-Hughes is a co-applicant on the NIHR-funded SAFEPIT and FReSH START trials and serves on the Data Monitoring Committees for the OCEAN, I-Minds, MILESTONE, MONITOR, SPEED and STORM trials. She also works as a design expert for the Yorkshire and North East Regional Advisory Committee for NIHR Research for patient benefit and is a protocol editor for Trials. Amanda J Farrin has been a member of NIHR CTU Standing Advisory Committee, HTA Efficient Study Designs Board, HTA Antimicrobrial Resistance Themed Call Board, HTA Clinical Evaluation and Trials Committee, HTA Funding Committee Policy Group, and Rapid Trials and Add-on Studies Board.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration and would be subject to review by a subgroup of the trial team, which will include the data guarantor, Professor Farrin. Access to anonymised data may be granted following this review. All data-sharing activities would require a data-sharing agreement.

Ethics statement

Informed consent was obtained from participants prior to entry into the trial. MODULATE was reviewed by and received ethical approval from the Yorkshire and the Humber, Leeds West Research Ethics Committee (reference 266428, approval dated 26 February 2020) and by the MHRA (CTA 16767/0301/001-0001, approval dated 9 January 2020), the Health Research Authority (IRAS 266428, approval dated 26 February 2020), and R&I departments for each participating site prior to entering participants into the trial. MODULATE was sponsored by the University of Leeds (GA19/105668).

Information governance statement

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management were brought to the attention of the TSC and, where applicable, to individual NHS trusts/health boards.

The trial was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996.

The University of Leeds organisation/institution is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Leeds is the Data Controller, and more information about how the data controller handles personal data, including how to exercise individual rights and the contact details for the data protection officer can be found here: https://dataprotection.leeds.ac.uk/

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Publications and papers

Moreau L, Taylor C, Brookes M, Graca S, Guthrie E, Houghton LA, *et al. Implementing a Remote Pathway and the Development of a Fully Decentralised Pathway in a Live Multi-arm, Multi-stage Complex Intervention Trial*. Poster session presented at the International Clinical Trials Methodology Conference (ICTMC), Harrogate, United Kingdom, 3–6 October 2022.

Cragg WJ, Taylor C, Moreau L, Collier H, Gilberts R, McKigney N, *et al.* Approaches and experiences implementing remote, electronic consent at the Leeds Clinical Trials Research Unit. *Trials*. 2024;25:310. https://doi.org/10.1186/s13063-024-08149-y

Trial registration

This trial is registered as ISRCTN16086699. https://doi.org/10.1186/ISRCTN16086699

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 17/33/03.

This synopsis provided an overview of the research award Management of diarrhoea in patients with stable ulcerative colitis: multi-arm multi-stage trial of low FODMAP diet, amitriptyline, ondansetron or loperamide (MODULATE). For more information about this research please view the award page (https://fundingawards.nihr.ac.uk/award/17/33/03).

About this synopsis

The contractual start date for this research was in April 2019. This article began editorial review in November 2023 and was accepted for publication in August 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

List of abbreviations

AE	adverse event
BDA	British Dietetic Association
BSG	British Society of Gastroenterology
CCUK	Crohn's and Colitis UK
CRF	case report form
CRP	C-reactive protein
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
FC	faecal calprotectin
FODMAP	fermentable oligo-, di-, and mono-saccharides and polyols
GP	general practitioner
GSRS-IBS	Gastrointestinal Symptom Rating Scale-IBS
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
IBD	inflammatory bowel disease
IBD-Q	Inflammatory Bowel Disease Questionnaire
IBS	irritable bowel syndrome
IMP	investigational medicinal product
MAMS	multiarm multistage
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OD	once daily
PI	principal investigator
PIS	participant information sheet
RCT	randomised controlled trial
RDE	remote data entry
REC	Research Ethics Committee
R&I	Research and Innovation
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressant
TMG	Trial Management Group
TSC	Trial Steering Committee
tTG	tissue transglutaminase
UC	ulcerative colitis

List of supplementary materials

Report Supplementary Material 1
MODULATE Participant Information Sheets

Report Supplementary Material 2
Treatment Dose Guidance Documents

Report Supplementary Material 3 IBS dietary advice sheet (modifiedBDA)

This synopsis should be referenced as follows:
Moreau LA, Ford AC, Brookes MJ, Graca S, Guthrie E, Hartley S, *et al.* Management of diarrhoea in patients with stable ulcerative colitis with low FODMAP diet, amitriptyline, ondansetron or loperamide: the MODULATE RCT [published online ahead of print March 12 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/GHFE4871

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/GHFE4871).

Supplementary material has been provided by the authors to support the report, and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

References

1. Timmer A, Patton PH, Chande N, McDonald JW, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;**2016**:CD000478. https://doi.org/10.1002/14651858.CD000478.pub4
2. Wang Y, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;**4**:CD000543. https://doi.org/10.1002/14651858.CD000543.pub4
3. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;**2016**:CD000544. https://doi.org/10.1002/14651858.CD000544.pub4
4. Gracie DJ, Williams CJ, Sood R, Mumtaz S, Bholah MH, Hamlin PJ, Ford AC. Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease. *Am J Gastroenterol* 2016;**111**:541–51. https://doi.org/10.1038/ajg.2016.59
5. Gracie DJ, Williams CJ, Sood R, Mumtaz S, Bholah MH, Hamlin PJ, Ford AC. Negative effects on psychological health and quality of life of genuine irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2017;**15**:376–84.e5. https://doi.org/10.1016/j.cgh.2016.05.012
6. Gracie DJ, Ford AC. Ongoing symptoms in ulcerative colitis patients in remission: irritable bowel syndrome or gastrointestinal symptoms in the absence of inflammation? *Inflamm Bowel Dis* 2017;**23**:E4–5. https://doi.org/10.1097/mib.0000000000000984
7. Williams CJ, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-alpha therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;**39**:447–58.
8. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2013;**108**:1268–76.
9. Lichtenstein GR, Rutgeerts P, Sandborn WJ, Sands BE, Diamond RH, Blank M, *et al*. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol* 2012;**107**:1051–63.
10. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, Cosnes J, *et al*. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617–25.
11. Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. *BMJ* 2015;**350**:h701. https://doi.org/10.1136/bmj.h701
12. Garsed K, Chernova J, Hastings M, Lam C, Marciani L, Singh G, *et al*. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut* 2014;**63**:1617–25. https://doi.org/10.1136/gutjnl-2013-305989
13. Ford AC, Lacy BE, Harris LA, Quigley EM, Moayyedi P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol* 2019;**114**:21–39.https://doi.org/10.1038/s41395-018-0222-5
14. Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2011;**2011**:CD003460.
15. Ford AC, Moayyedi P, Chey WD, Harris LA, Lacy BE, Saito YA, Quigley EMM; ACG Task Force on Management of Irritable Bowel Syndrome. American College of Gastroenterology monograph on management of irritable bowel syndrome. *Am J Gastroenterol* 2018;**113**:1–18.
16. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut orocaecal transit times in health and irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;**8**:159–66.
17. Talley NJ, Phillips SF, Haddad A, Miller LJ, Twomey C, Zinsmeister AR, *et al*. GR 38032F (ondansetron),

a selective 5HT3 receptor antagonist, slows colonic transit in healthy man. *Dig Dis Sci* 1990;**35**:477–80.

18. Sun WM, Read NW, Verlinden M. Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scand J Gastroenterol* 1997;**32**:34–8.
19. Pedersen N, Ankersen DV, Felding M, Wachmann H, Vegh Z, Molzen L, *et al*. Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease. *World J Gastroenterol* 2017;**23**:3356–66. https://doi.org/10.3748/wjg.v23.i18.3356
20. Macer BJ, Prady SL, Mikocka-Walus A. Antidepressants in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2017;**23**:534–50. https://doi.org/10.1097/mib.0000000000001059
21. Mikocka-Walus A, Hughes PA, Bampton P, Gordon A, Campaniello MA, Mavrangelos C, *et al*. Fluoxetine for maintenance of remission and to improve quality of life in patients with Crohn's disease: a pilot randomized placebo-controlled trial. *J Crohns Colitis* 2017;**11**:509–14. https://doi.org/10.1093/ecco-jcc/jjw165
22. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, *et al*.; IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011;**60**:571–607.
23. National Institute for Health and Care Excellence. *Ulcerative Colitis: Management in Adults, Children and Young People*. 2013. URL: www.nice.org.uk/guidance/cg166/evidence/full-guideline-pdf-190220365 (accessed 1 November 2023).
24. Svedlund J, Sjodin I, Dotevall G. GSRS – a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988;**33**:129–34.
25. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;**96**:804–10.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
27. Rogler G, Aldeguer X, Kruis W, Lasson A, Mittmann U, Nally K, *et al*. Concept for a rapid point-of-care calprotectin diagnostic test for diagnosis and disease activity monitoring in patients with inflammatory bowel disease: expert clinical opinion. *J Crohns Colitis* 2013;**7**:670–7. https://doi.org/10.1016/j.crohns.2013.02.014
28. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, *et al*. Association of Coloproctology for Great B, Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;**59**:666–89. https://doi.org/10.1136/gut.2009.179804
29. Department of Gastroenterology and Department of Nutrition and Dietetics Guy's and St Thomas' NHS Foundation Trust, Department of Nutritional Sciences King's College London . Reducing Fermentable Carbohydrates the Low FODMAP Way. In Department of Gastroenterology and Department of Nutrition and Dietetics GSTNFT, Department of Nutritional Sciences KCL, editors; 2020.
30. Department of Gastroenterology and Department of Nutrition and Dietetics Guy's and St Thomas' NHS Foundation Trust, Department of Nutritional Sciences King's College London . Suitable Products for the Low FODMAP Diet. In Department of Gastroenterology and Department of Nutrition and Dietetics GSTNFT, Department of Nutritional Sciences KCL, editors; 2020.
31. Department of Gastroenterology and Department of Nutrition and Dietetics Guy's and St Thomas' NHS Foundation Trust, Department of Nutritional Sciences King's College London . Reintroducing FODMAPS. In Department of Gastroenterology and Department of Nutrition and Dietetics GSTNFT, Department of Nutritional Sciences KCL, editors; 2020.
32. King's College London. *King's College London Low FODMAP Education Courses for Health Professionals*. 2023. URL: www.kcl.ac.uk/slcps/our-departments/fodmap (accessed 1 November 2023).
33. Julious SA. Seven useful designs. *Pharm Stat* 2012;**11**:24–31. https://doi.org/10.1002/pst.485
34. Probert CJ, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott IDR, Forbes A. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003;**52**:998–1002.
35. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005;**54**:782–8. https://doi.org/10.1136/gut.2004.056358
36. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, *et al*. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol* 2007;**102**:794–802. https://doi.org/10.1111/j.1572-0241.2007.01094.x
37. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, *et al*. Quality of life: a valid and reliable

measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994;**106**:287–96.

38. (MHRA) MaHpRA. *MHRA Performance Data for Assessment of Clinical Trials and Established Medicines*. 2022–2023 [cited 2023]. URL: www.gov.uk/government/publications/mhra-performance-data-for-assessment-of-clinical-trials-and-established-medicines (accessed 1 November 2023).
39. James Lind Alliance. *James Lind Alliance Priority Setting Partnership in Inflammatory Bowel Disease*. 2022 [cited 2023]. URL: www.jla.nihr.ac.uk/priority-setting-partnerships/inflammatory-bowel-disease/ (accessed 1 November 2023).
40. Murray K, Wilkinson-Smith V, Hoad C, Costigan C, Cox E, Lam C, *et al*. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol* 2014;**109**:110–9. https://doi.org/10.1038/ajg.2013.386
41. Major G, Pritchard S, Murray K, Alappadan JP, Hoad CL, Marciani L, *et al*. Colon hypersensitivity to distension, rather than excessive gas production, produces carbohydrate-related symptoms in individuals with irritable bowel syndrome. *Gastroenterology* 2017;**152**:124–33.e2. https://doi.org/10.1053/j.gastro.2016.09.062
42. O'Keeffe M, Jansen C, Martin L, Williams M, Seamark L, Staudacher HM, *et al*. Long-term impact of the low-FODMAP diet on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization in irritable bowel syndrome. *Neurogastroenterol Motil* 2017;**30**:e13154. https://doi.org/10.1111/nmo.13154
43. Barrett JS, Gibson PR. Development and validation of a comprehensive semi-quantitative food frequency questionnaire that includes FODMAP intake and glycemic index. *J Am Diet Assoc* 2010;**110**:1469–76. https://doi.org/10.1016/j.jada.2010.07.011

Appendix 1 Interventions

Low fermentable oligo-, di-, and mono-saccharides and polyols diet intervention

FODMAP is an acronym for '**f**ermentable **o**ligo-, **d**i-, and **m**ono-saccharides **a**nd **p**olyols'. These are short-chain carbohydrates that are not absorbed well in the small intestine. This means that they are subsequently fermented by bacteria in the large intestine, which produces gas, leading to bloating and flatulence. This phenomenon is normal and is common to everyone. However, more pronounced gastrointestinal symptoms can develop from FODMAPs when the bowel response is exaggerated or abnormal, such as in the case of people with IBS.[40,41] Most FODMAPs occur naturally in foods within the human diet. However, they can be added artificially during the commercial production of foods and drinks.

TABLE 4 Low FODMAP diet delivery

Appointment	Timescale and method	Details of appointment
Dietitian appointment 1	Within 1 week of randomisation, via video call, telephone or in-person	Education provided to each participant covering the mechanistic actions of FODMAPs in the gut, high FODMAP-containing food sources to avoid, and medium and low levels that can be included per meal session, including suitable food products to include in their diet. Educational booklets (copyright Guy's and St Thomas' NHS Foundation Trust and King's College London) are provided to participants via post prior to the appointment. They can also contact the dietitian about any uncertainties relating to implementation of the diet.
Dietitian appointment 2	After 8 weeks on the low FODMAP diet, via video call, telephone or in-person	The dietitian will determine whether the patient has positively responded to the intervention by assessing adherence to the low FODMAP diet and whether overall gastrointestinal symptoms have improved. Those who do not report satisfactory overall symptom relief or those who are unable to adhere to the low FODMAP diet will return to their usual diet.[a] Responders will progress to the next two stages of the diet: the reintroduction and personalisation stages. The dietitian will counsel the participant on structured, dosed reintroduction of individual FODMAPs, using the third booklet as an aid.
Telephone review	At week 16, via telephone	At week 16, all responders will receive a telephone call to discuss the FODMAP reintroduction and to encourage study retention and dietary adherence. Dietitians will support participants with their understanding of FODMAP personalisation (increasing dietary and nutritional variety while maintaining symptom control).
Dietitian and/or nurse appointment 3	After 24 weeks, via video call, telephone or in-person	After 24 weeks, those participants judged to be responders at the 8-week appointment will receive a final approximately 30-minute appointment. For all responders, this will be with a dietitian, and a further appointment will be organised with the research nurse to complete the remaining trial assessments. For non-responders to the low FODMAP diet at 8 weeks, only the appointment with the research nurse for final data collection will take place.

a Adherence at 8 weeks and 6 months will be determined using a 4-point- Likert scale[42] (scored 1 – continued a strict low FODMAP diet; 2 – reintroduced high FODMAP foods to tolerance; 3 – continued a low FODMAP diet 50% of the time; 4 – returned to habitual diet). Analysis of FODMAP content will be via the Comprehensive Nutrition Assessment Questionnaire (CNAQ)[43] in all participants, in order to verify that the FODMAP content is less in the low FODMAP diet arm at 8 weeks, compared with the other four trial arms. The CNAQ is a semiquantitative food frequency questionnaire validated to assess FODMAP and nutrient intake, and is determined using an online automated entry system www.monashfodmapcalculator.com.au/). Participants who are classed as non-adherent after the 8-week restriction phase will be classed as non-responders and will be instructed to return to their usual diet. This will include participants who do not respond with an answer of 1, 2 or 3 to the adherence question.

Appendix 2 End points

Primary end point

Phase 2

Improvement in diarrhoea was defined as scoring ≤ 2 on the diarrhoea subscale of the GSRS-IBS,[24] indicating minor discomfort from diarrhoea or less. The GSRS-IBS is a validated questionnaire, used widely in trials of medical therapies in gastrointestinal diseases.[24] It is a 13-item self-administered questionnaire measuring the presence and severity of gastrointestinal symptoms, which are measured on a 7-point Likert scale, defined by descriptive anchors (no discomfort at all; minor discomfort; mild discomfort; moderate discomfort; moderately severe discomfort; severe discomfort; or very severe discomfort). The higher the scores, the more pronounced the symptoms.

Phase 3

The IBD-Q is a validated questionnaire, designed to measure disease-specific quality of life in people with IBD.[25] The questionnaire has 32 items, which are grouped into four domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional factors (12 items) and social factors (5 items). Each item is scored on a 7-point Likert scale, ranging from 1 (worst of health) to 7 (best of health). The total IBD-Q score therefore ranges from 32 to 224, with higher scores reflecting better quality of life.

Secondary outcome measures (at 8 weeks and 6 months post randomisation)

Loose stools, diarrhoea, urgency and abdominal pain

The GSRS-IBS[24] was used to assess the effect of the various interventions on discomfort from loose stools,

urgency, discomfort from diarrhoea and abdominal pain at both 8 weeks and 6 months.

Disease activity

Data concerning need for either escalation of medical therapy for UC or surgery were collected as a binary measure by research nurses from patient records at each participating centre at 8 weeks and 6 months, using a standardised CRF, which was supplemented by patient questionnaires collecting these data. Participants also provided blood for CRP (measured in mg/l) and stool for FC (measured in mcg/g) at 6 months only, which were both to be collected as continuous measures.

Mood

The HADS is a well-validated, commonly used, self-report instrument for detecting anxiety and depression in people with medical illnesses.[26] It comprises seven items measuring anxiety, and seven measuring depression. Higher scores indicate more severe anxiety or depression.