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MODULATE

Management **o**f **d**iarrhoea in **u**lcerative colitis: multi-arm multi stage trial of **l**ow FODMAP diet, **a**mitriptyline, ondanse**t**ron, or lop**e**ramide: **MODULATE**

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This protocol has regard for the HRA guidance

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1. ABBREVIATIONS

Abbreviation	Explanation
AE	adverse event
AR	adverse reaction
BDA	British Dietetic Association
CI	chief investigator
CNAQ	Comprehensive Nutrition Assessment Questionnaire
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	C-reactive protein
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
FBC	full blood count
FC	faecal calprotectin
FODMAP	fermentable olig-, di-, and mono-saccharides and polyols
GCP	Good Clinical Practice
GP	general practitioner
GSRS-IBS	Gastrointestinal Symptom Rating Scale-IBS
HADS	Hospital Anxiety and Depression Scale
IBD-Q	Inflammatory Bowel Disease Questionnaire
IBS	irritable bowel syndrome
ID	identification
IME	important medical event
IMP	investigational medicinal product
MAMS	multi-arm multi-stage
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	NICE National Institute for Health and Care Excellence
OD	once daily
PI	principal investigator
PIC	Participant Identification Centre
PIS	participant information sheet
RCT	randomised controlled trial
REC	research ethics committee
RGF	Research Governance Framework
RSI	reference safety information
RUSAE	related unexpected serious adverse event
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard deviation

SOP	standard operating procedure
SPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressants
TMG	Trial Management Group
ToR	terms of reference
TSC	Trial Steering Committee
tTG	tissue transglutaminase
UC	ulcerative colitis

TRIAL SUMMARY

Title	**M**anagement **o**f diarrhoea in **u**lcerative colitis: multi-arm multi stage trial of **l**ow FODMAP diet, **a**mitriptyline, ondanse**t**ron, or lop**e**ramide
Short title	MODULATE
Chief Investigator	Professor Alexander Ford
Trial design	Pragmatic, seamless, phase 2/3, open, parallel group, multi-arm multi-stage (MAMS) randomised controlled trial (RCT), with internal pilot.
Background	In participants with ulcerative colitis (UC), residual problems of diarrhoea and urgency during periods of stable disease can still affect participants. However, the best treatments for these symptoms, which can have both substantial negative physical and emotional impact, is unclear.
Target sample size and setting	A maximum of 491 participants (396 in phase 2 and up to 95 in phase 3) from approximately 26 secondary care settings.
Duration	25 months recruitment (including 12-month internal pilot) and 12 months follow-up.
Patient population	Inclusion criteria: ≥18 years; stable UC with at least moderate discomfort from diarrhoea according to the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) questionnaire (equating to a score of ≥4 on the diarrhoea subscale), C-reactive protein (CRP) <5mg/L, faecal calprotectin (FC) <250mcg/g and endoscopic Mayo score >1 at sigmoidoscopy (if performed due to clinical uncertainty). Exclusion criteria: Previous or planned gastrointestinal surgery; active UC (CRP ≥5mg/L, FC ≥250mcg/g or endoscopic Mayo score >1 at sigmoidoscopy (if performed due to clinical uncertainty or rectal bleeding)); BMI≤18.5kg/m^2; steroids within the last 2 months; coeliac disease; previous colorectal cancer or dysplasia; allergy/contraindication to, or previous failed trial of, study interventions; pregnancy/breastfeeding. **Please refer to section 5 for the full list of inclusion and exclusion criteria.**
Intervention:	Participants will receive one of the following active interventions for 6 months: 1. Low fermentable oligo-, di-, and mono-saccharides and polyols (FODMAP) diet for 8 weeks, with FODMAP reintroduction to tolerance for the remaining 4 months for longer term symptom response. This will be administered by a dietitian already specially trained in delivering the low FODMAP dietary intervention, via four sessions (three face-to-face, and one via the telephone). 2. Low-dose amitriptyline. This will be commenced at a dose of 10mg (one tablet) at night, and dose titration will occur, to a maximum of 30mg once

<table>
<tr><td></td><td colspan="2">daily (OD) at night (three tablets), depending on side effects and response to treatment.

3. Ondansetron. This will be commenced at a dose of 4mg OD, and dose titration will occur, to a minimum of 4mg every week if constipation occurs, or a maximum of 24mg per day, depending on side effects and response to treatment.

4. Loperamide. Participants will be given the option to commence at a dose of 4mg per day, with dose titration occurring up to a maximum of 16mg per day, or to use this on an as required basis, depending on side effects and response to treatment.

5. Control intervention - standard first-line dietary advice, in the form of the British Dietetic Association (BDA) food fact sheet for people with irritable bowel syndrome (IBS), which is endorsed by the National Institute for Health and Clinical Excellence.

Participants in all active intervention arms will also receive the BDA food fact sheet for people with IBS. They will be advised not to alter their diet in any other way, unless they are in the low FODMAP diet arm of the trial. Once participants are recruited, they will be asked not to adjust or change any other over-the counter or prescribed medications for their UC.

Please refer to section 8 for full details of the interventions.</td></tr>
<tr><td>Randomisation</td><td colspan="2">Randomisation will be carried out by the Clinical Trials Research Unit (CTRU). Randomisation will be via minimisation at the level of the individual, stratified according to centre, degree of discomfort from diarrhoea, extent of UC, and Hospital Anxiety and Depression Scale (HADS)-Depression score.

During the phase 2 period participants will be randomised in the ratio 1:1:1:1:2, with the larger group receiving the control intervention. During the phase 3 period this will be reversed to 2:1, or 2:2:1, depending on the number of active interventions taken forward.</td></tr>
<tr><td rowspan="2"></td><td>Objectives</td><td>Outcome Measures</td></tr>
<tr><td>Primary: phase 2</td><td>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 symptoms?</td><td>GSRS-IBS questionnaire at 8 weeks post-randomisation: improvement defined as those reporting minor discomfort from diarrhoea or less (scoring ≤2 on the diarrhoea subscale).</td></tr>
</table>

Primary: 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?	Inflammatory Bowel Disease Questionnaire overall score at 6 months post-randomisation (measuring bowel symptoms, systemic symptoms, emotional, and social factors).
Secondary: phase 2 and 3. .	a. What is the effect of the active treatments, compared with a control of standard first-line dietary advice, in terms of improvement in discomfort from loose stools, diarrhoea, urgency, and abdominal pain? b. Markers of disease activity, including escalation of medical therapy, need for surgery, FC, and CRP? c. Improvement in the participants overall mood?	All secondary outcomes are measured at both 8 weeks and 6 months: a. GSRS-IBS; b. Blood for CRP, stool for FC at 6 months only, reviewing case notes for escalation of medical therapy for UC; c. HADS.
Other outcomes of interest	What is the safety and tolerability of the active treatments?	Safety assessed through collection of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest. Tolerability assessed via drop-out rates due to AEs, rates of constipation collected via the GSRS-IBS, and confirmed flares of disease activity at 8 weeks and 6 months. Drop-out rates in the low FODMAP arm for any reason pertaining to the intervention will also be taken into account when assessing tolerability.

	What is the adherence to each of the active treatments, compared with a control of standard first-line dietary advice?	Adherence to IMP (amitriptyline, ondansetron, loperamide) at 6 months is measured by self-report on the participant questionnaires (see section 13.3.10). Adherence to low FODMAP diet at 8 weeks and 6 months is determined using a 4-point Likert scale: • Adherence is defined as a Likert response of 1, 2, or 3 (4 is defined as not adherent).

2. BACKGROUND

2.1 Ulcerative Colitis

Ulcerative colitis is an inflammatory bowel disease. 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, research from our group has shown that symptoms do not always predict inflammatory activity, [4] and that 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 co-morbidity 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 this strategy is effective. In addition, inappropriate use of immunosuppressant drugs and biological therapies is expensive, and carries a risk of serious side effects, like opportunistic infection or malignancy. [7-10]

2.2 Intervention Strategies That Are Effective in Irritable Bowel Syndrome with Diarrhoea

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 anti-emetic ondansetron, [12] which is a 5-HT_3 receptor antagonist, low-dose tricyclic antidepressants (TCAs), [13, 14] such as amitriptyline, and the anti-diarrhoeal drug loperamide. [15] All these drugs can slow colonic transit. [16-18]

2.3 Evidence for Efficacy of these Intervention Strategies in Patients with Ulcerative Colitis

The evidence base for the use of any of the proposed treatments in patients with stable UC with diarrhoea is not strong. There has been one 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 recent systematic review concluded that low-dose antidepressants may have a positive impact on the natural history of inflammatory bowel disease, [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 have been no RCTs of ondansetron or loperamide in this group of patients with UC, and patients with ongoing diarrhoea often receive conflicting advice about the safety and effectiveness of the latter drug in UC, despite the fact that it is available over-the-counter. It is 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 make 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.

2.4 MODULATE Trial

Given that the specific mechanism of diarrhoea is unclear in this group of patients with UC, assessing more than one of these therapies in a trial maximises the efficiency of the design. MODULATE is a pragmatic, multi-centre, efficient, adaptive, multi-arm multi-stage (MAMS) RCT to determine the individual effectiveness of these three drugs and a low FODMAP diet in the treatment of diarrhoea in patients with stable UC.

There is no standard care pathway for patients with stable UC with diarrhoea. There have been RCTs of some treatments that are used in irritable bowel syndrome conducted in patients with inflammatory bowel disease, including antidepressants, probiotics, and psychological therapies, [21, 24, 25] but none have recruited only patients with confirmed stable UC and ongoing diarrhoea, so effectiveness in this population remains uncertain.

2.5 Potential Benefits

The results from MODULATE will be important for clinicians, patients, and health service planners, and should help them to make better-informed decisions regarding the management of diarrhoea in patients with stable UC in secondary care.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Aims

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.

3.2 Primary Objectives

Our primary objectives are 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 Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) [26] at 8 weeks, defined as reporting minor discomfort (score ≤2) from diarrhoea or less.

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 Inflammatory Bowel Disease Questionnaire (IBD-Q) [27] at 6 months?

3.3 Secondary Objectives

Our secondary objectives are 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 (i) loose stools, (ii) diarrhoea, (iii) urgency, and (iv) abdominal pain, each assessed via the GSRS-IBS [26]?
    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) [28]?

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?

3.4 Internal Pilot Objectives

Pre-defined progression criteria will assess trial progression after approximately 6/12 months of recruitment with respect to rates of:

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

4. STUDY DESIGN

4.1 Design

A pragmatic, seamless, phase 2/3 open label, parallel group MAMS RCT of low FODMAP diet, titrated low-dose amitriptyline, titrated ondansetron, loperamide either taken on demand or titrated, or standard first-line dietary advice for the treatment of diarrhoea in patients with stable UC in secondary care. The trial will include an internal 12-month pilot with clear progression criteria for recruitment, treatment drop-out, adherence to a low FODMAP diet, and follow-up rates.

The study aims to recruit a maximum of 491 adult patients with stable UC in secondary care who still report at least moderate discomfort from diarrhoea (equating to a score of ≥4 on the diarrhoea subscale of the GSRS-IBS). Randomisation will be stratified according to study centre, the degree of discomfort from diarrhoea, extent of UC and HADS-Depression score.

Participants and personnel delivering the intervention will not be blind to the treatment allocation. Outcome assessment using self-report methods (postal or online) is planned, based on participant preference.

4.2 Treatment Regimens

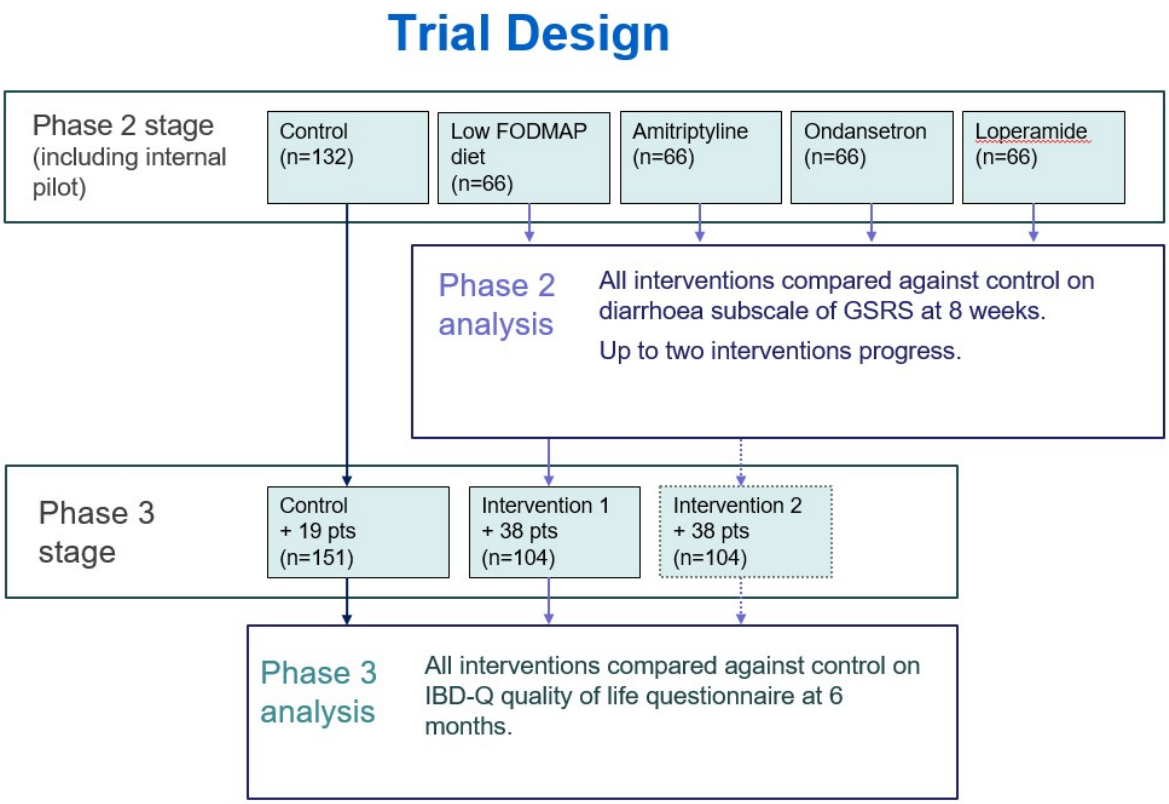
Patients will be randomised to receive a low FODMAP diet, titrated low-dose amitriptyline, titrated ondansetron, loperamide either taken on demand or titrated, or a control intervention of standard first-line dietary advice, all for 6 months. All drugs will be titrated, according to differing regimens, and depending on the individual's response to treatment and side effects. Please see section 8 for treatment details.

4.3 Phase 2 to Phase 3 Transition

Phase 2 will evaluate the short-term effectiveness of all active interventions, each compared with a control of standard first-line dietary advice at 8 weeks, in terms of improvement in diarrhoea, via the diarrhoea subscale of the GSRS-IBS. Analysis will be performed when sufficient patients have reported 8 week GSRS-IBS outcome data and a maximum of two of the interventions showing evidence of short-term effectiveness will continue to phase 3 to evaluate longer-term effectiveness in terms of improved disease-specific quality of life, via the IBD-Q at 6 months post-randomisation.

There will be a temporary halt to active recruitment of approximately 3-4 months after approximately 396 participants are recruited to phase 2, to allow for analysis prior to progression to phase 3. We expect to require 19 months of recruitment to recruit these first 396 patients, meaning that all data for the 8-week time point should be collected by month 21.

Figure 1 Summary of Trial Design



4.4 Internal Pilot

An internal pilot, across a minimum of 10 centres, will assess recruitment, treatment drop-outs, adherence to a low FODMAP diet, and follow-up rates. Rates will be monitored monthly by the Trial Management Group (TMG), to identify, proactively, centres below target requiring additional support to improve progress.

Progression criteria are:

Recruitment rates will be assessed after 6 months of recruitment. Rates will be calculated from recruitment in each of the 6 sites in months 4 to 6 to allow time for recruitment to stabilise:

 Green/Continue: At least 80% of target recruitment (>80% of 1.4 pts/site/month)
 Amber/Review: 50%–80% of target recruitment rate
 Red/Stop: Less than 50% of target recruitment rate

Treatment drop-out will be assessed 6 months later, i.e. after 12 months of recruitment:
 Green/Continue: No more than 20% of patients withdraw from any one of the active treatments
 Amber/Review: No more than 40% of patients withdraw from any one of the active treatments
 Red/Stop: More than 40% of patients withdraw from one or more the active treatments

Adherence to a low FODMAP diet will be assessed after 12 months of recruitment:
 Green/Continue: At least 80% of patients adhere to diet
 Amber/Review: 60-80% of patients adhere to diet
 Red/Stop: Less than 60% of patients adhere to diet

Follow-up rates will be assessed after 12 months of recruitment
 Green / continue: At least 80% follow-up
 Amber / review: 60-80% follow-up
 Red/stop: Less than 60% follow-up

If any criteria are amber, we will review trial processes comprehensively and develop a rescue plan, approved by the Trial Steering Committee (TSC), which will be submitted to the HTA. If the treatment drop-out or adherence criteria are red, this will result in the relevant treatment arm(s) being dropped from the trial. If the recruitment or follow-up criteria are red, the TSC will consider not progressing the pilot to the definitive trial.

4.5 Participating Sites

Participants will be recruited from approximately 26 centres in secondary care across the UK. Research centres will be identified via a feasibility assessment to determine the most appropriate centres to participate in the trial. The participating centres will receive training provided by the CTRU and trial dietitian, provide confirmation of capacity and capability, and sign the model non-commercial agreement prior to the start of recruitment to the trial.

Potentially eligible patients will also be identified by primary care general practitioners (GPs) and other secondary care hospitals, working as participant identification centres (PICs) who will be responsible for the identification of potential patients for the trial, but will retain responsibility for the healthcare of the patients outside the research.

5. ELIGIBILITY CRITERIA

Eligible patients who take part in the study must meet all of the inclusion criteria and none of the exclusion criteria. Eligibility waivers to inclusion/exclusion criteria are not permitted.

5.1 Inclusion Criteria

1. A histological diagnosis of UC in secondary care, including left-sided colitis or extensive colitis.
2. Age ≥18 years.
3. At least moderate discomfort from diarrhoea according to the GSRS-IBS [26] (equating to a score of ≥4 on the diarrhoea subscale of the GSRS-IBS)
4. On stable doses of UC-related medication for ≥2 months at time of initial screening telephone call.
5. Ongoing diarrhoea for 3 months prior to initial screening telephone call.
6. A CRP <5mg/L (measured as per local practise) within 4 weeks prior to randomisation.
7. FC <250mcg/g [29] within 4 weeks prior to randomisation.
8. Stable UC at the time of randomisation, in the clinical opinion of the gastroenterologist[1],
9. No evidence of active suicidal ideation at time of initial screening telephone call and prior to randomisation, as determined by the three clinical screening questions below[2]:
    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?
10. No recent history of self-reported self-harm (an episode of self-harm within the last 12 months).
11. Willing to be considered for all treatment arms of the trial, and to remain in the treatment arm to which they are assigned.
12. If female must be:
    a. post-menopausal (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 [IMP]). [3]
13. Able to complete questionnaires and trial assessments.
14. Able to provide written informed consent.

5.2 Exclusion Criteria

1. Inflammatory bowel disease 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 (tTG) antibodies).
7. A previous diagnosis of colorectal dysplasia or cancer, or no up to date surveillance colonoscopy, as per current British Society of Gastroenterology guidelines [30].
8. Known allergy to TCAs, ondansetron, or loperamide.
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.[4]
12. Contraindications[5] 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 Q-T 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[6].

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[1] A flexible sigmoidoscopy with Mayo score ≤1 is only required if there is clinical uncertainty regarding the stability of the patient's UC and is at the discretion of the treating physician. Rectal bleeding reported by the patient would contribute to the assessment of disease stability and if present should be assessed by flexible sigmoidoscopy.
[2]Suicidal ideation should be assessed on the screening telephone call. No more than 14 days should elapse between the initial suicidal ideation assessment and study entry/ randomisation. If more than 14 days have elapsed then the suicidal ideation assessment should be repeated.
[3]Highly effective contraception is defined as one of the following: combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with

inhibition of ovulation (oral, injectable, or implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; practising true abstinence (defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject).

[4]Patients currently waiting to see a dietitian for a low FODMAP diet must agree not to commence seeing a dietitian unless they are randomised to the low FODMAP arm of the trial.

[5]Cautions to the use of TCAs will not be an exclusion, but these will be recorded at screening and clarified with the patient's gastroenterologist and the principal investigator (PI) in each centre prior to study entry. These include cardiovascular disease; diabetes; epilepsy; history of psychosis or bipolar disorder; hyperthyroidism; increased intra-ocular pressure; phaeochromocytoma; prostatic hypertrophy (prostate gland enlargement); susceptibility to angle-closure glaucoma; difficulty passing urine.

[6] For women of childbearing potential (those not post-menopausal or surgically sterile) a pregnancy test must be performed within 7 days prior to randomisation. Post-menopausal is defined as no menses for 12 months without an alternative medical cause.

6. Recruitment Process

6.1 Patient Identification

Secondary Care

Potential patients will be identified in standard clinics and will be approached about the trial by a member of the attending clinical team, and then provided with verbal and written details.

Patients will also be identified by searching existing, relevant, clinic lists and hospital databases for patients with stable UC. Those that report diarrhoea, without objective evidence of disease activity, will be contacted by telephone or letter to inform them about the trial, and to invite them to take part in an initial telephone screening call. The local PI or delegate will check the list of patients prior to contact, to ensure that it is appropriate to contact them.

Postal invitations will include an invite letter, the participant information sheet (PIS), contact details of the research team, and a reply slip. Patients interested in taking part in the study will return the reply slip or contact the research team.

In order to alert existing patients to the study we will display posters and/or leaflets in clinic waiting areas and any other appropriate location(s). With permission from consultant colleagues, patients will be sent an invite letter and patient flyer with their out-patient appointment letter. This letter will include a brief introduction to the study and patients will be invited to ask further questions at their next scheduled visit, or to contact the MODULATE research team for further details.

Where suitable, information about the study will be included on relevant websites and research databases that can be accessed by members of the public with UC who are interested in opportunities to take part in research. This information will include a brief synopsis of the study and details of which centres are participating in the study. Interested parties will be directed to enquire about the study at their next appointment at the clinic or to contact the consultant / nurse specialist at their local hospital.

The NIHR BioResource platform will be used to alert patients in the proximity of participating centres to the study. Patients would be sent a flyer with information about the study and directed to enquire about the study at their next clinic appointment or to contact the consultant / nurse specialist at their local hospital.

Primary Care and Pharmacies

Potentially eligible patients will also be identified by primary care GPs and local pharmacies, working either as PICs or a source of trial advertising (see below). PICs will be responsible for the identification of potential patients for the trial and referral to the nearest recruiting site for formal study screening. GP practices will retain responsibility for the healthcare of the patients outside the research and will be notified of a patient's participation.

Trial Information / Advertising

All MODULATE advertising material will direct potential patients to the MODULATE website, which will contain all the patient information documentation for the study. The website will also contain an ethically approved self-screening questionnaire that will ask a series of questions that will help the potential patient to assess their eligibility for the trial.

If the self-screening questionnaire indicates that the patient may be eligible, they will be directed to a form that asks them to provide details for contact by their local research nurse. Once submitted, the contact details form will be automatically forwarded to the MODULATE email inbox, where the research team will review the address provided and assess whether there is a site open currently in the participant's local area. If so, the contact details will be forwarded to that site and the research nurse will contact the participant to begin the registration process. Alternatively, patients will be able to view sites currently open for recruitment on the 'More Information' page of the MODULATE website and may choose to contact their local site directly for more information.

The MODULATE trial will be advertised using a series of poster and leaflets, as well as on IBD special interest websites, such as the Crohn's and Colitis UK website. Promotional material will be distributed to relevant locations at site, as well as, but not limited to, GP practices, community pharmacies, and local support groups. Details will be provided of how to contact the local research team or self-screening form in one of the participating research sites for

further information so that interested patients can arrange an appointment to further assess their eligibility.

A specific MODULATE trial Twitter account accessed by CTRU staff only will be used to advertise the trial to allow potential participants to become aware of the trial. Tweets used for the purpose of recruitment into the trial will be ethically approved prior to use.

In addition, the study team will utilise an ethically approved video to explain and promote the trial. The video will be available on various websites, including the CTRU website and relevant social media platforms website. It will also be distributed to local Clinical Research Networks and support groups.

Where possible, the trial team will engage with local and national newspapers to increase publicity about the trial.

If potentially eligible, patients will be invited to a formal eligibility assessment at one of the participating research sites, which will take on the responsibility for seeking consent and undertaking trial research procedures.

6.2 Eligibility Screening

Potential participants will be identified by the clinical team at participating centres, based on their diagnosis of UC. Each trial research site will be required to maintain a log of all participants screened for eligibility, including those who are not recruited either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- age
- gender
- ethnicity
- how they heard about the trial
- reason for ineligibility for trial participation or;
- reason for declining participation

Screening logs must be sent to the CTRU every month or on request.

6.3 Telephone Screening

The research nurse or authorised delegate at each participating centre, will obtain verbal consent to telephone-screen potential participants who express an interest in taking part in the study using a questionnaire consisting of the GSRS-IBS (diarrhoea question only), and questions about the inclusion and exclusion criteria. After initial telephone screening, if the participant is potentially eligible the research nurse will inform the participant they will post out a stool sample kit to their home address to allow the participant to bring in a stool sample to their consent visit.

Any individual expressing suicidal ideas will be excluded from the trial and referred to their GP for formal assessment of their mood and mental health.

6.4 Informed Consent

The local PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate, according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

Verbal consent will be obtained prior to the telephone screening. Informed consent will be obtained prior to the participant undergoing procedures after the telephone screen that are specifically for the purposes of the study and are out-with standard routine care at the participating site, where a test has been performed as part of local care, and is within the required timeframe, it does not have to be repeated.

Participants who are potentially eligible, after telephone screening, will be asked to attend an appointment at their local participating centre. At this visit the investigator, or authorised delegate, will discuss the trial in detail with the patient, providing a comprehensive overview of the study including the background, purpose, and the risks and benefits of participation. The investigator will explain that all treatment arms offer potential therapeutic benefits, and confirm that the patient still expresses a desire to enter the study, regardless of the treatment arm they are assigned to, and will remain in that arm for the duration of the study.

Patients will have as long as they need (at least 24 hours, unless the participant wishes to participate sooner) to consider participation, and will be given the opportunity to discuss the study with their family and healthcare professionals before they are asked whether they would be willing to take part. If the patient requires more time to consider participation, and/or discuss with family and other healthcare professionals, consent can be obtained at the next visit, prior to any trial assessments being performed.

The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study, without giving reasons and without prejudicing his/her further treatment. The participant must also be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

Information provided to participants will also include the potential to collect longer term routine data, should further funding become available.

Where the patient is able to provide full informed consent but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team.

A record of the consent process detailing the date of screening call, consent and all those present will be kept in the participant's medical notes. The original signed and dated informed consent form(s) will be filed in the Investigator Site File, a copy will be given to the participant, a copy will be returned to the CTRU, and another copy will be filed in the hospital notes (as per local practice).

All participants who consent will be registered into the trial.

6.5 Loss of Capacity

Where valid informed consent is obtained from the patient, and the patient subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Patients who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the PI and patient's carer / family with the patient's best interests foremost in the decision-making process. Ongoing collection of safety and follow-up data (where possible, and with support of the research team at site where appropriate) will continue via the clinical care team for inclusion in the trial analysis, in order to preserve the integrity of the trial's analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

6.6 Role and responsibilities of IBD Nurse Specialists

IBD 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 qualification and training, MODULATE will extend the following roles to IBD Nurse Specialists:

Principal investigator:

IBD Nurse Specialists can assume the role of PI for a site provided they meet the following criteria:

- Clinical Nurse Specialist (CNS), specialising in IBD
- Informed consent trained
- Good Clinical Practice trained
- Local NHS Trust Standard Operating Procedures allow for the extension of the role of PI of a CTIMP to non-medical clinicians.

A medically-trained doctor will still be required to confirm eligibility prior to randomisation and to assess causality and expectedness of SAEs/SUSARs.

Prescribe IMP and review new medications:

IBD Nurse Specialists who are non-medical prescriber-qualified can prescribe trial IMP and review new medications on-trial to confirm that they are not restricted or prohibited medications.

Take Informed Consent:

IBD Nurse Specialists may take informed consent provided that they are

- Informed consent trained
- Good Clinical Practice trained

Local NHS Trust Standard Operating Procedures allow for the extension of the role of informed consent to non-medical clinicians in CTIMPs.

6.7 Registration

Following confirmation of written informed consent, patients will be registered into the trial by an authorised member of staff at the local research site. Registration will be performed centrally using the CTRU registration service via a web-based system; which provides an automated, secure, 24-hour service. User names and PINs/passwords will be provided by the CTRU and will be required to access the registration and randomisation system.

The following information will be required at registration:

- Username (for web)
- Personal 4 digit PIN/password
- Name of research study site and site 5 digit code
- Patient initials and date of birth
- Confirmation of written informed consent

Web address for 24-hour registration: https://lictr.leeds.ac.uk/webrand/

At the point of registration participants will be issued a unique trial number. This unique five digit number together with the centre number will form the participant identification (ID) number.

After trial registration the research site will:

- Add the unique participant ID number to all case report forms (CRFs);
- Return a copy of the completed consent form to CTRU;
- Provide the participant with a patient flyer containing a trial ID card;
- Provide participants with their appointment dates;
- Book a flexible sigmoidoscopy appointment (if required due to clinical uncertainty as to whether the patient's UC is stable).

Following participant registration, CTRU will email confirmation of registration to the research team and pharmacy at site.

6.8 Screening Assessments

After registration, patients will undergo the following assessments to confirm eligibility

- CRP (results must be <5mg/L within 4 weeks prior to randomisation)
- FC (must be <250mcg/g within 4 weeks prior to randomisation)
- Anti-tTG to exclude coeliac disease;
- In the case of clinical uncertainty regarding the stability of the patient's UC, patients may be required to undergo a limited flexible sigmoidoscopy (phosphate enema to prep) to confirm mucosal remission (endoscopic Mayo score ≤1),
- Assessment of Body Mass Index (must not be ≤18.5kg/m^2 at screening)
- Pregnancy test for women of childbearing potential (those not post-menopausal or surgically sterile) (test must be within 7 days prior to randomisation).

If blood and stool results, and sigmoidoscopy (if deemed necessary by the treating physician), are all normal as defined above, the patient will be required to complete a baseline questionnaire pack remotely, undertake a home pregnancy test (if hospital screening visit was >7 days prior to randomisation) and then be randomised by the CTRU.

In the case of an abnormal blood result for CRP, which may be a temporary abnormality (e.g. secondary to a recent infection), the blood test may be repeated approximately 1-2 weeks later if the participant wishes to undertake further screening for the study.

If the blood (or repeat blood test) or stool tests show an abnormal result the individual will be referred back to his or her gastroenterologist for further assessment and will not be randomised into the study.

6.9 Randomisation

6.8.1 Timing of Randomisation

Prior to randomisation patients must have provided full informed consent, previously been registered onto the MODULATE trial, confirmed as being eligible by a medically-trained doctor, and completed the baseline assessments. **It is important that baseline assessments are performed prior to randomisation, as the HADS-D score is used as a stratification factor.** Randomisation will be performed centrally using the CTRU 24-hour randomisation service (see below for process), and take place as soon as possible after consent and eligibility are confirmed.

6.8.2 Treatment Allocation

For both phase 2 and phase 3, randomisation will be via minimisation at the level of the individual, stratified according to:

- Centre;
- Degree of discomfort from diarrhoea (score ≥5) ;
- Extent of UC (left sided or extensive);
- Depression via HADS-Depression score (score ≥8).

Phase 2 randomisation: participants will be randomised in the ratio 1:1:1:1:2, with the larger group receiving the control intervention.

Phase 3 randomisation: participants will 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.

6.8.3 Randomisation Process

Participants will be randomised by the research nurse, or another authorised member of the research team via a web address based at the CTRU. For the web address randomisation, site staff email address, site code, and PIN will be required. The person accessing the web address to randomise the participant must have the completed randomisation CRF available at the time of accessing the web, as the following information will be required:

- Username (for web);
- Personal 4 digit PIN/password;
- Name of research study site and site 5 digit code;
- Date of birth;
- Participant's unique trial number provided at registration;
- Confirmation of eligibility;
- Confirmation of completion of baseline assessments;
- Confirmation of participant completion of baseline questionnaires;
- Degree of discomfort from diarrhoea via GSRS-IBS;
- Extent of UC: left sided or extensive;
- Baseline HADS-D score.

DIRECT LINE FOR 14-HOUR RANDOMISATION Online Access: https://lictr.leeds.ac.uk/webrand/

6.8.4 Post-randomisation Actions

After trial randomisation the research site will:

- Ensure the participant's trial ID card is updated with their treatment allocation. The participant should be 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 trial.
- Ensure that participants are notified of any appointment dates.
- Notify the participant's GP of their participation in the trial using the approved study GP letter.

Following participant randomisation, CTRU will email a participant randomisation notification to the research team and pharmacy or dietitian depending on allocation.

Participants must begin their trial treatment within 1 week of being randomised.

6.10 Gift Vouchers

Participants will receive a gift voucher after randomisation. The value of the gift voucher will differ depending on which intervention the patient has been allocated to. This is because the number of visits to the hospital, and therefore potential inconvenience, differs across the intervention arms.

Those randomised to either the control, loperamide or ondansetron arm will receive a £20 voucher. Those randomised to either the low FODMAP or amitriptyline arm will receive a £30 voucher.

7. INVESTIGATIONAL MEDICINAL PRODUCTS

7.1 Investigational Medicinal Products

Within the trial, the following are classed as IMPs:

Amitriptyline

Composition: 10mg oral tablets.

Generic ('off the shelf') commercial supplies to be used. Please refer to the most recent summary of product characteristics (SPC).

Ondansetron

Composition: 4mg oral tablets.

Generic ('off the shelf') commercial supplies to be used. Please refer to the most recent SPC.

Loperamide

Composition: 2mg oral capsules.

Generic ('off the shelf') commercial supplies to be used. Please refer to the most recent SPC.

For further details of composition of the IMPs used in this trial, refer to the current version of the manufacturer's SPC, which can be accessed via the Electronic Medicines Compendium website: http://www.medicines.org.uk/emc. A reference copy of the SPCs can be found in the Investigator and Pharmacy Site Files; please note however that these may not necessarily be the most up-to-date versions.

7.2 IMP Formulation, Storage, and Preparation

Formulation, storage and preparation of the IMPs are in line with the manufacturers' recommendations. For further details, refer to the current version of the relevant manufacturer's SPC (via http://www.medicines.org.uk/emc). There is no requirement to ring-fence 'off the shelf' supplies of the IMPs.

7.3 IMP Preparation

All IMPs will be prepared and handled in line with manufacturers' recommendations.

7.4 IMP Labelling

Pharmacy will be responsible for labelling amitriptyline, ondansetron, and loperamide in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994. As all three medications are being used outside their licensed indication, the CTRU will provide additional, approved trial-specific labels in accordance with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). The information on the study specific labels will include:

a) Name and address of the Sponsor;
b) Chief investigator (CI) name;
c) EudraCT number;
d) For Clinical Trial Use only;
e) Space for adding the patient's trial ID number.

Trial specific labels will be provided to pharmacy as pre-printed labels or in electronic format to be printed by pharmacy, depending on local pharmacy preference.

Please refer to the Pharmacy and IMP Study Site Operating Procedure for full details of the trial IMP management requirements.

7.5 IMP Dispensing

The batch number, expiry date and quantity of all amitriptyline, ondansetron, and loperamide dispensed, date of dispense and how issued to the participant should be recorded on the trial specific dispensing and accountability log found within the pharmacy site file.

7.6 IMP Delivery to Participants

Dispensed trial IMP can be collected by the participant from the participating trial site.

Alternatively, trial IMP may be posted to the participant by Royal Mail Signed For® delivery, via courier to their home address or in line with local practice for postage of medications (see section 12 for risk assessment).They will be posted at ambient temperature without temperature monitoring. The date the IMP was posted to the participant should be recorded and confirmation that the participant has received the medication should be sought by the site and recorded.

7.7 IMP Destruction

Unused study medication should be returned to pharmacy for destruction. This is to ensure any unused medication is removed from the community and safely disposed of. A full reconciliation (tablet count) will not be performed, since this is a pragmatic trial and the self-titration of dose by participants in response to their symptoms and side effects would render the information difficult to interpret. The key concern is to safely remove the medication from the community. Returned IMP should be destroyed by site pharmacy as per local practice.

IMP that has been dispensed to a participant must not be re-dispensed to a different participant.

8. TREATMENT DETAILS

8.1 Low FODMAP Diet

8.1.1 Overview

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 [31, 32] Most FODMAPs occur naturally in foods within the human diet. However, they can be added artificially during the commercial production of foods and drinks.

Participants randomised into the low FODMAP diet arm of the study will be instructed to restrict intake of fructans, galacto-oligosaccharides, polyols, lactose, and fructose (high levels, or where fructose is in excess of glucose) until the end of week 8. This restriction process will be guided by counselling from a specialist gastroenterology dietitian, who has adequate experience in treating patients with IBS-like symptoms on the low FODMAP diet.

If participants see an improvement in their symptoms after 8 weeks they will continue onto FODMAP reintroduction. During this stage, participants will reintroduce FODMAP sub groups separately whilst maintaining an otherwise low FODMAP diet.

After reintroduction, the dietitian can then interpret the participant's specific FODMAP triggers and work towards establishing a long-term personalised FODMAP diet. This involves fully re-introducing FODMAPs that are tolerated well, and only restricting foods that triggered symptoms.

The dietitian sessions will take place at each site's usual outpatient dietetic clinic room setting. Education and resources and support given to each participant should help them to incorporate the low FODMAP restriction into their daily activities at home. Participant height and weight will be recorded on the first visit, and weight will be recorded at each further face to face visit.

8.1.2 Dietitian Identification

Dietitians who are familiar with delivering the low FODMAP diet to gastroenterology patients with IBS like symptoms will be identified to deliver the intervention. During site identification, the length of time dietitians have been counselling on the low FODMAP diet will be recorded. Dietitians will also be expected to have King's College accreditation, or have been suitably trained by someone who has. It is anticipated that one dietitian will be trained at each site. We do not require dietitians to be GCP trained as the will be carrying out standard of care duties only.

8.1.3 Dietitian Training

To minimise inter-dietitian variation and enhance fidelity, dietitians will receive detailed intervention training in remote training sessions. Training will be delivered by the Lead Trial Dietitian using the site's preferred video calling platform. Training is limited to a single workshop as the intervention is readily learned by trained National Health Service (NHS) dietitians who are familiar with delivering the low FODMAP diet to people with IBS-like symptoms. Ongoing training and support will be provided as required, and will be documented.

Intervention training will include an explanation of the roles of site research staff, the resources to be used in intervention delivery, and any additional research tasks which they will be expected to complete. Supervision of dietetic staff will be by usual NHS line management.

Details of training provision, including content, attendance, and duration will be documented. Intervention dietitians will have access to training materials to support intervention delivery.

8.1.4 Delivery of intervention

Dietitian Appointment 1 (within 1 week of randomisation)

In the first session with the dietitian, education will be given 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. Two written comprehensive educational booklets (copyright Guy's and St Thomas' NHS Foundation Trust and King's College London) will be used which will be given to each participant to take home. More details on these resources can be found in the TiDIER checklist, Appendix 1. Dietary counselling will involve practical information on meal and snack ideas in line with healthy eating principles, meal planning, recipe modification, reading food labels, eating out tailored to the participant, and consolidation of what was discussed. To support dietary adherence, participants will be encouraged to review the information provided during the session at home and plan grocery shopping, meals, and snacks to incorporate the low FODMAP restriction into their daily activities.

Dietitian Appointment 2

After 8 weeks on the low FODMAP diet (**the restriction stage**), each participant will attend a second face-to-face 30-minute session held at the site's usual outpatient dietetic clinic room setting.

In this session the dietitian will decide 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 respond or adhere to the low FODMAP diet will return to their usual diet. Those who respond to the low FODMAP dietary intervention will progress to the next stage of the diet, **the reintroduction stage,** and will receive a third booklet outlining the process of reintroduction and personalisation**.** If more convenient, the third booklet may be supplied to the participant at Dietitian Appointment 1 with the first two comprehensive booklets and participants advised not to use the third booklet until their 8-week Dietitian Appointment 2. The dietitian will advise the participant on when to reintroduce FODMAP subgroups, the quantity of food to reintroduce, and the ordering of reintroduction. This is done to help increase dietary variety whilst keeping diarrheal symptoms under control.

Telephone Review

At week 16, halfway through this reintroduction phase, 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 FODMAP personalisation (increasing dietary and nutritional variety whilst maintaining symptom control) if participants have completed the reintroduction process.

Dietitian and/or Nurse Appointment 3

After 24 weeks, each participant will return for a final 30-minute face-to-face session at the site's usual outpatient dietetic clinic room setting to reassess dietary adherence. For all responders, this will be with a dietitian and research nurse. For non-responders to the low FODMAP diet, this will be with the research nurse only for final data collection.

8.1.5 Monitoring Participant Adherence

Adherence at 8 weeks and 6 months will be determined using a 4-point- Likert scale [33] (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) [34] 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 semi-quantitative food frequency questionnaire validated to assess FODMAP and nutrient intake, and is determined using an online automated entry system (http://www.cnaq.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 any participants who do not respond with an answer of 1, 2, or 3 to the adherence question.

8.1.6 Monitoring Intervention Fidelity

In order to ensure that the low FODMAP dietary intervention is delivered as intended consistently across sites, fidelity will be monitored using a bespoke fidelity check list. This check list covers three domains of setting, knowledge of content, and competency of delivery. This check list will be self-completed by dietitians at all visits, with a random sample of ~10% being assessed to ensure consistency and competency across sites.

8.2 Amitriptyline

8.2.1 Dosage and Duration

Participants randomised to receive amitriptyline will begin treatment at a low dose of 10mg (one tablet) to be taken once daily (OD) at night. Self-led dose titration may occur during the first three weeks of treatment depending on side effects and response to treatment, using the dose guidance document provided. The dose can be increased by 10mg OD per week, to a maximum of 30mg OD at night (three tablets), if there is inadequate improvement in symptoms and no intolerable side effects. Therefore, participants will take 10mg OD for the first week. They may then increase to 20mg OD for the second week. A final increase to 30mg OD could be made in the third week. Treatment with amitriptyline will continue for a total of 6 months.

8.2.2 Dose Modification

After the first 3 weeks it is expected that most participants will continue on a steady dose of drug. However, the dose of amitriptyline can be modified throughout the study in response to side effects and to achieve normalisation of stool consistency and improvement of discomfort associated with diarrhoea. We expect most participants to find a dose that it suitable for them between 10mg OD and 30mg OD, but participants will be allowed to reduce their dose further, to 10mg every other day if they continue to experience troublesome side effects at 10mg OD. The maximum dose that patients will be allowed to take is 30mg OD. Standardised guidance on dose titration and modification will be provided to participants.

8.2.3 Assessment of Amitriptyline Adherence

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

8.2.4 Amitriptyline Supply and Assessments

Participants will receive an initial 1-month supply of amitriptyline. This should allow for the maximum titration of amitriptyline in this time period. At each telephone call the research nurse should check to make sure there have been no changes to the participant contact details.

Week 1 Telephone Call:

Participants will be called at week 1 by their research nurse to deal with any queries and provide standardised advice about dose titration.

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since randomisation;
    - Concomitant medications check;

Week 3 Telephone Call:

Participants will be contacted by their research nurse by telephone at 3 weeks, to confirm the dose reached during titration and to ensure that there are no contraindications to further medication being issued.

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since week 1;
    - Concomitant medications check;
    - Suicidal ideation check: If there is any evidence of suicidal ideation, the participant must stop taking amitriptyline, no further amitriptyline should be issued and their GP should be informed of the need for urgent review to assess their mood and mental health;
    - Confirm participant contact details;
    - Arrange for a further 2 months of trial treatment to be supplied, if appropriate.

Participants will be offered a review with their gastroenterologist (either via telephone or face-to-face) at approximately 1 month, for safety purposes (in relation to taking the study drug), if the research nurse or patient have any queries or concerns.

Month 3 Telephone Call:

A further telephone call from the research nurse will take place just before 3 months, to ensure that there are no contraindications to further medication being used.

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since week 8;
    - Concomitant medications check;
    - Suicidal ideation check: If there is any evidence of suicidal ideation, the participant must stop taking amitriptyline, no further amitriptyline should be issued and their GP should be informed of the need for urgent review to assess their mood and mental health;
    - Confirm participant contact details;
    - Arrange for a final 3 months of trial treatment to be supplied, if appropriate.

At each telephone call the research nurse should check to make sure there has been no changes in the participant contact details.

8.2.5 Amitriptyline Toxicity

The most frequent anticipated toxicities of amitriptyline are as follows:

Aggression	Somnolence
Dizziness	Dry mouth
Headache	Constipation
Drowsiness	Nausea

For a full list of toxicities please refer to the latest SPC for amitriptyline.

8.3 Ondansetron

8.3.1 Dosage and Duration

Participants randomised to receive ondansetron will start on an initial dose of 4 mg (one capsule), OD. If symptoms do not improve then self-led dose titration may occur during the first 2 weeks on treatment. Participants will be given a dose guidance document to support self-titration and will also receive a telephone call from a research nurse on day 7 to offer support. The dose can be increased by 4mg (one capsule) every 2 days until a stable dose is achieved. The maximum dose of ondansetron is 8 mg three times per day (24mg per day, or six capsules daily). After the first 2 weeks the patient should continue on a steady dose of drug, unless a further change is required to achieve normalisation of stool frequency, as confirmed by discussion between the patient and the research team. Treatment with ondansetron will continue for a total of 6 months.

8.3.2 Dose Modification

The dose of ondansetron can be modified throughout the study to achieve normalisation of stool consistency and improvement of discomfort associated with diarrhoea. If a patient experiences constipation, they must stop taking ondansetron until a bowel movement occurs, and then restart at a lower dose. If required, the dose will be reduced to a minimum of one tablet per week. Participants unable to tolerate these minimal doses should discontinue ondansetron. Standardised guidance on dose titration and modification will be provided to participants.

8.3.3 Assessment of Ondansetron Adherence

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

8.3.4 Ondansetron Supply and Assessments

Participants receiving ondansetron will be provided with an initial 3-month supply of ondansetron. This should allow for the maximum titration of ondansetron in this time period. At each telephone call the research nurse should check to make sure there have been no changes to the participant contact details.

Week 1 Telephone Call:

Participants will be called at week 1 by their research nurse to deal with any queries and provide standardised advice about dose titration.

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since randomisation;
    - Concomitant medications check;

Week 3 Telephone Call:

Participants will be contacted by their research nurse by telephone at 3 weeks, to confirm the dose reached during titration

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since week 1;
    - Concomitant medications check;
    - Confirm participant contact details.

Participants will be offered a review with their gastroenterologist (either via telephone or face-to-face) at approximately 1 month, for safety purposes (in relation to taking the study drug),, if the research nurse or patient have any queries or concerns.

Month 3 Telephone Call:

A further telephone call from the research nurse will take place just before 3 months, for safety purposes, before a further 3 months of ondansetron can be dispensed.

- Information to be collected:

- Dose of study medication;
- Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since week 8;
- Concomitant medications check;
- Confirm participant contact details;
- Arrange for a final 3 months of trial treatment to be supplied, if appropriate

8.3.4 Ondansetron Toxicity

For a full list of toxicities please refer to the latest SPC for Ondansetron. The most common side effect for ondansetron is constipation.

8.4 Loperamide

8.4.1 Dosage and Duration

Participants randomised to receive loperamide will be given the option to use this as required, or to commence on 4mg per day (two capsules), and self-titrate the dose upwards to a maximum of 16mg per day (eight capsules), depending on symptoms, using the dose guidance document provided. Treatment with loperamide will continue for a total of 6 months.

8.4.2 Dose Modification

Participants can either use loperamide as required or modify their dose throughout the study, as desired, to achieve normalisation of stool consistency and improvement of discomfort associated with diarrhoea. Standardised guidance on dose titration and modification will be provided to participants.

8.4.3 Assessment of Loperamide Adherence

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

8.4.4 Loperamide supply and Assessments

Participants receiving loperamide will be provided with an initial 3-month supply of trial medication. This should allow for the maximum titration of loperamide in this time period.

At each telephone call the research nurse should check to make sure there have been no changes to the participant contact details.

Week 1 Telephone Call:

Participants will be called at week 1 by their research nurse to deal with any queries and provide standardised advice about dose titration.

- Information to be collected:
  - Dose of study medication;
  - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since randomisation;
  - Concomitant medications check;

Week 3 Telephone Call:

At week 3, participants will be contacted by their research nurse by telephone to confirm the dosing strategy adopted by the participant (PRN or titrated) and the dose reached at the end of the titration period.

- Information to be collected:
    - Dose of study medication;
    - Dosing strategy (PRN or titrated);
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since week 1;
    - Concomitant medications check;
    - Confirm participant contact details.

Participants will be offered a review with their gastroenterologist (either via telephone or face-to-face) at approximately 1 month, for safety purposes (in relation to taking the study drug), if the research nurse or patient have any queries or concerns.

Month 3 Telephone Call:

A further telephone call from the research nurse will take place just before 3 months, for safety purposes, before a further 3 months of loperamide can be dispensed.

- Information to be collected:
    - Dose of study medication;
    - Toxicity assessment: collection of SAEs/SARs/SUSARs experienced since week 8;
    - Concomitant medications check;
    - Confirm participant contact details;
    - Arrange for a final 3 months of trial treatment to be supplied, if appropriate

8.4.4 Loperamide Toxicity

For a full list of toxicities please refer to the latest SPC for Loperamide.

The most common side effect for loperamide is constipation. If this happens participants should reduce their dose as per the dose guidance document. Loperamide may increase the risk of developing toxic megacolon in patients with inflammatory bowel disease, although this is very unlikely in patients with stable disease. However, participants are advised to contact their doctor/research nurses urgently if they develop abdominal (tummy) pain, fever, and a racing heart.

8.5 Standard Clinical Practice (All Arms)

All participants will continue their usual treatment for UC during the trial, and will be provided with the BDA IBS dietary advice sheet https://www.bda.uk.com/foodfacts/IBSfoodfacts.pdf), which is NICE-endorsed. They will be advised not to alter their diet in any other way, unless they are in the low FODMAP diet arm of the trial.

8.6 Concomitant Treatments

The use of prohibited and restricted concomitant medications will be reviewed prior to confirmation of eligibility according to section 5. Patients that are unable to stop taking prohibited medication will be unable to enter the study. Concomitant medication reviews will also take place on the week 1, week 3, and month 3 telephone calls, and confirmation that the patient is not taking any prohibited or restricted medication will be recorded on the CRF. It is the responsibility of the local PI (or delegate) to review any new concomitant medication at the study visit to confirm the patient's continuing suitability for the study.

Use of monoamine oxidase inhibitors (e.g. selegiline and moclobemide) and drugs that prolong the QT interval (e.g. amiodarone, terfenadine, or sotalol) are prohibited for the participant for the duration of the trial.

For management of concomitant therapies, please refer to the latest SPCs for amitriptyline, ondansetron and loperamide. Concomitant medications started prior to the study will be allowed to continue at a stable dose providing, in the opinion of the investigator, they are not likely to alter bowel habit or are prohibited (see section 5).

If participants require treatment for another non-gastrointestinal condition, their PI (or medically-trained doctor in sites with an IBD Nurse Specialist PI without a prescribing qualification) will review the new drug therapy to consider whether there is a risk that the drug may affect gastrointestinal symptoms. If this agent is deemed unlikely to influence gastrointestinal symptom reporting they will be allowed to commence it. However, if any new treatment is deemed to have a high chance of influencing gastrointestinal symptom reporting, then instances of this will be recorded and monitored, in order to assess whether there are equal rates among arms of the trial.

Use of loperamide in all non-loperamide arms of the study (amitriptyline, ondansetron, low FODMAP diet and control) is not permitted throughout the duration of the study.

As loperamide is available as an 'over the counter' medication as a well-known remedy for diarrhoea (Immodium) and participants are made aware of all the interventions used across the study, loperamide usage will be monitored across all non-loperamide arms.

8.6 Treatment After Study Participation

Following participation in the study, subsequent patient care will be decided by their consultant gastroenterologist, according to usual practice.

8.7 Discontinuation of Study Treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians, or the participants themselves. All participants who discontinue from treatment, or who are prescribed alternative treatment, will still attend for follow-up assessments and complete questionnaires, unless they withdraw from the trial (see section 10). Data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. The reason for discontinuing study medication will be recorded. Reasons for study treatment discontinuation include:

- Patient decision;
- Severe non-compliance to this protocol as judged by the investigator;
- Safety, including allergic reaction to IMP;
- If the investigator considers that a patient's health will be compromised due to AEs or concomitant illnesses that develop after entering the study;
- Receipt of a restricted concomitant medication after entering the study;
- Pregnancy;
- Overdose;
- Suicidal ideation;
- Flare of disease activity.

Once study medication is permanently discontinued it cannot be restarted as part of the study. Patients should return all unused IMP on cessation of trial treatment. If a participant withdraws from treatment, a Treatment Discontinuation CRF should be completed by the site.

9. ASSESSMENTS AND DATA HANDLING

9.1 Data Collection

Data will be collected for all participants registered to the MODULATE trial. Data will be collected by Remote Data Entry (RDE) on electronic Case Report Forms (eCRFs) managed by the CTRU at the University of Leeds. Access to the live MODULATE database will be provided by the CTRU following site being authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided.

Paper CRFs and participant questionnaires will also be provided for some assessments. Questionnaires completed electronically will be via 1) REDCap electronic patient-reported outcome software 2) an online automated entry system for the CNAQ data http://www.cnaq.com.au (see below). Paper CRFs will be provided electronically by the CTRU at the University of Leeds.

CRFs must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific authorised personnel log. The original 'wet ink' version of the completed CRFs should be returned to CTRU by fax or Secure File Transfer (SFT). Copies of the completed CRFs should be retained by the site and stored in the investigator site file (or a statement of their location). All data queries, notifications and requests for information should be sent to modulate@leeds.ac.uk.

The original copy of the consent form must be filed in the investigator site file and a photocopy faxed or securely emailed using SFT to CTRU.

It is the responsibility of staff at research sites to redact all personal identifiable data, with the exception of the participant consent form, where the participant name and signature must not be redacted. For all other CRFs, patient identifiers will be used to identify the patient as follows; trial number, initials, and date of birth.

9.1.1 Participant Questionnaires – Process Overview

All participants will be asked to complete questionnaires at the following time points:

Baseline – participants must be provided with either a paper questionnaire booklet in the post or a link for the REDCap system via text and/or email to complete the questionnaire online prior to randomisation.

8 weeks – participants can opt to complete the 8-week questionnaire online or on paper. For those choosing the paper questionnaire a booklet containing all the questionnaires will be posted directly to the participant's home address by CTRU.. Participants who chose to complete online assessment will be sent a link to the REDCap system via text and/or email to complete the remaining 8-week questionnaires,

6 months – participants can opt to complete the 6-month questionnaire online or on paper. For those choosing the paper questionnaire this must be completed by the participant when they attend their 6-month face-to-face visit.

Participants who choose to complete online assessments will be sent a link to the REDCap system via text and/or email to complete the 6-month questionnaires. If participants have not completed them by the time they attend the 6-month face-to-face visit, they should complete them on paper during this visit.

9.2 Assessments

9.2.1 Schedule of Events

A tabulated summary of all assessments is provided in Appendix 5

9.2.2 Treatment Arm Specific Assessments – Overview

For full details of the treatment specific assessments please see section 8 and the Schedule of Events. In summary:

Control Group: no additional assessments

Low FODMAP Arm:

- Face-to-Face appointments with the dietitian during week 1 and after week 8 for participants randomised to this arm.
- Telephone call (16 weeks) and face-to-face appointment (24 weeks) with dietitian for responders only. All participants (including non-responders) will also see a research nurse at 24 weeks as per section 9.2.2 below.

Drug Intervention Arms:

- Telephone calls from the research nurse at weeks 1 and 3, and month 3, post-randomisation. Please refer to the treatment specific guidance provided for each individual study drug in section 8 for details.
- Participant diary cards – participants to record the number the number of tablets they have taken each day on diary cards from start to completion of study treatment. The diary cards are to be used as participant guidance so participants can monitor their own adherence to medication.

Assessments to be carried out for all patients in all arms are detailed below in section 9.2.3.

9.2.3 Baseline Assessments – All Participants

Prior to randomisation the following baseline information will be collected by a member of the research team for all patients:

- socio-demographic details;
- current medication;
- past medical history and medications;
- duration and extent of UC;
- previous or current psychiatric diagnoses.
- Suicidal ideation

Prior to randomisation all potential participants must complete either a paper baseline questionnaire and assessment booklet sent in the post or an online questionnaire and assessment booklet accessed via REDCap, consisting of:

- Discomfort from loose stools, diarrhoea, urgency, and abdominal pain on the GSRS-IBS [26];
- Disease-specific quality of life via the IBD-Q [27];
- HADS [28];
- CNAQ [34]: nutrient and FODMAP intakes will be quantified via a validated food frequency questionnaire, the Monash University CNAQ. This measures intake of energy, carbohydrate, protein, fat, dietary fibre, total FODMAPs, fructans, GOS, polyols as sorbitol and mannitol, fructose, excess fructose, and lactose.

9.2.2.1 8-week Assessments- All Participants

9.2.2.1.1 Patient Reported Questionnaires

Participants will self-complete a postal or web-based questionnaire, depending on individual preference, at 8 weeks post-randomisation. They will be sent an SMS reminder and an email to prompt completion. If participants are completing paper questionnaires, their research nurse will call them to prompt completion one-week from the date of postage. If questionnaires have not been completed within 1 week of the reminder, a further reminder will be sent 1 week later, and the study team will attempt to contact the participant to collect data for the primary and secondary endpoint over the telephone.

For the low FODMAP arm patients should complete these questionnaires before commencing the reintroduction phase.

Questionnaires will include:

- GSRS-IBS [26];
- IBD-Q [27];
- HADS [28];
- Need for either escalation of medical therapy for UC or surgery;
- CNAQ [34].

9.2.2.1.2 Data Collection from Medical notes

The following data will be collected from the medical notes and recorded on the CRF:

- Confirmed flare of disease activity;
- Any requirement for escalation of UC-related medical therapy;
- Need for surgery.
- Collection of SAEs/SARs/SUSARs/RUSAEs experienced since randomisation;

9.2.2.2 6-month Face-to Face visit- All Participants

9.2.2.2.1 Patient Reported Questionnaires

Participants will self-complete a questionnaire booklet at 6 months post-randomisation. Participants completing questionnaires online will be sent the questionnaire via text message and/or email. Participants completing questionnaires on paper will be sent the questionnaire via post; the research nurse will contact the participants at 6 months to remind them to complete the booklets and return them. They will be sent an SMS reminder and an email to prompt completion. If the questionnaire has not been completed by the time the participant attends the 6-month face-to-face visit, they will be asked to complete it at the visit on paper.

Questionnaires will include:

- GSRS-IBS [26];
- IBD-Q [27];
- Tolerability;
- HADS [28];
- Need for either escalation of medical therapy for UC or surgery;
- CNAQ [34] (low FODMAP arm only).

9.2.2.2.2 Face-to-Face Visit

At 6 months, participants will be invited to a final face-to-face appointment with a research nurse. Prior to this visit a stool sample collection kit should be sent to the participant.

The following assessments/data collection will be undertaken at face-to-face visit:

- Blood for CRP;
- Stool for FC;
- Any requirement for escalation of UC-related medical therapy;

- Need for surgery;
- Confirmed flare of disease activity.
- Dose of study medication for IMP arms
- SAE/SAR/SUSAR/RUSAE check
- Concomitant medications check.

9.2.3 CNAQ

Nutrient and FODMAP intakes will be quantified via a validated food frequency questionnaire. This will be the Monash University Comprehensive Nutrition Assessment Questionnaire, CNAQ). Participants will be provided with a paper version to record quantities of food they habitually consume. This will measure intake of energy, carbohydrate, protein, fat, dietary fibre, total FODMAPs, fructans, GOS, polyols as sorbitol and mannitol, fructose, excess fructose, and lactose. The CNAQ will be participant completed at baseline and week 8 by all participants. The CNAQ will also be completed at week 24 for participants in the low FODMAP arm. The goal is for each participant on the diet to achieve a total FODMAP intake of no more than 12g per day by week 8 during the restriction stage.

9.4 Archiving Trial Data and Documents Held by CTRU

At the end of the trial, all data held by the CTRU and all trial data will then be securely archived, in line with the Sponsor's procedures, for a minimum of 25 years. Data held by the CTRU will be archived in the University of Leeds archive facility and site data and documents will be archived at the participating centres.

Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed.

9.5 Definition of End of the Trial

The end of the trial is defined as the date of the collection of the last participant's 6-month data collection item.

10. WITHDRAWAL CRITERIA

Withdrawal from trial treatment is separate from withdrawal from the trial/data collection (see section 8.7). The PI, or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented, using the withdrawal CRF, in order that the correct processes are followed by the CTRU and site following the withdrawal of consent. The withdrawal CRF should be returned to CTRU within 24 hours of the research team at the site becoming aware. It should be made clear to any participant specifically withdrawing consent for further data collection in a CTIMP that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. Data already collected will be retained.

In addition, the site should make the participant aware of the fact that, if any significant new information becomes available in regard to the treatment they have received in the trial, it may be necessary to contact them in the future.

Patients who withdraw from the trial follow-up would not need to complete further participant questionnaires. Reasons for withdrawal from the follow-up assessments would include:

- Patient decision;
- Lost to follow-up;
- Death.

11. PHARMACOVIGILANCE

11.1 General Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions

Adverse Event

An AE is any untoward medical occurrence (including deterioration of a pre-existing medical condition) in a patient or clinical trial patient administered a trial treatment / procedure, and which does not necessarily have a causal relationship with this treatment and can include:

- Any unintentional, unfavourable clinical sign or symptom (including an abnormal laboratory finding, for example);
- A symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)

An AR is any untoward and unintended response to an IMP related to any dose administered. This definition implies a reasonable possibility of a causal relationship, which is supported by facts, evidence, or arguments to suggest a causal relationship. This definition includes medication errors, and uses of the IMP outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

Serious Adverse Event / Serious Adverse Reaction (SAR)

A SAE is any untoward medical occurrence or effect that at any dose:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Other important medical event (IME)***.

** "Life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

*** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).*

****IMEs are events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant, or may require intervention to prevent one of the other outcomes listed in the definitions above.*

Medical judgement should be exercised in deciding whether an AE is serious. These characteristics must be considered at the time of the event, and do not refer to an event that may hypothetically have caused one of the above. Where an SAE is deemed to have been related to an IMP used within the trial, the event is termed a SAR. Any suspected transmission via an IMP of an infectious agent is also considered a SAR.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
A SUSAR is a serious adverse drug reaction that also demonstrates the characteristic of being unexpected, the nature, seriousness, severity, or outcome of which is not consistent with the information about the IMP, as set out in the reference safety information (RSI).

Related Unexpected Serious Adverse Event (RUSAE)

A RUSAE is a serious event that is related, in that it occurs from the administration of any of the research procedures, however it was unexpected as the type of event is not listed in the protocol as an expected occurrence. RUSAEs are reportable in the non-CTIMP arms of the trial only.

11.2 MODULATE Operational Definitions

The safety profile of all the IMPs in MODULATE are well known. It is therefore not the intention of this study to collect all AEs. The occurrence of reportable AEs will be self-reported by the participant on the participant questionnaires at 8 weeks and 6 months for patients in all arms. Only the confirmation of occurrence and corresponding severity (mild-noticeable but not preventing normal activities, moderate-restricting some activities, severe- preventing any activities) will be recorded. SAEs, SARs, and SUSARs will be collected for the duration of the trial. The following AEs will be collected:

- Constipation;
- Abdominal pain / bloating (as part of the condition being treated);
- Headache;
- Nausea;
- Vomiting;
- Rectal bleeding:
- Dizziness

- Drowsiness
- Dry mouth
- Insomnia

11.2.1 Adverse Events / Adverse Reactions and Serious Adverse Events / Serious Adverse Reactions

For general definitions of AEs, ARs, SAEs and SARs, please see section 11.1 above.

When determining whether a SAE or SAR is expected or not, please refer to section 4.8 of the current RSI SPC, for the relevant IMP which is provided in the Investigator Site File.

11.2.2 Events Not Classified as an SAE in the MODULATE trial

The following events will not be recorded as SAEs within this study:

Hospitalisation for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition;
- Treatment that was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition;
- Admission to hospital or other institution for general care, not associated with any deterioration in condition;
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious, as given above, and not resulting in hospital admission.

11. 2.3 Adverse Events of Special Interest

Constipation

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 must undergo immediate investigation as follows:

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

If the CRP and/or the FC results are abnormal (CRP ≥5mg/L, FC ≥250mcg/g), the patient will have a limited flexible sigmoidoscopy to assess for evidence of mucosal inflammation. If both CRP and FC are normal it is at the treating physician's discretion, in consultation with the

participant, to decide whether a limited flexible sigmoidoscopy is still required. If flare of disease activity is confirmed after sigmoidoscopy (endoscopic Mayo score >1), this is classed as an AE of special interest and will be expedited to the CTRU for review on the Flare CRF within 24 hours of the site confirming the event. The patient's trial treatment will be discontinued, and they will be referred back urgently to their responsible gastroenterologist for appropriate management.

Self-harm or Suicide

Any reported form of self-harm, or suicide, will be treated as an IME and reported to the CTRU within 24 hours of the site becoming aware of the event on an SAE form.

11.3 MODULATE Reporting Requirements

All SAEs, SARs, and SUSARs will be collected from time of consent up to 7 days after the last dose of IMP. All SAEs and SUSARs should be reported to the CTRU within 24 hours of the site becoming aware of the event. If sites become aware of any SARs or SUSARs occurring after this active monitoring period, these must still be reported in an expedited manner **up to 90 days after the end of trial**.

The following details will be collected for each SAE:

- Place the SAE started;
- Full details in medical terms with a diagnosis, if possible;
- Duration (date of onset and date of resolution);
- The arm that the patient was randomised to on study;
- Seriousness criteria;
- Causality, in the opinion of the PI or delegate;
- Local opinion on expectedness as defined by the trial supplied RSI, if applicable;
- Action taken with regard to study medication, if applicable;
- Outcome.

In addition to the above the following details will be collected for each SUSAR:

- Relevant medical history;
- Concomitant medications;
- Treatment for SUSAR;
- Relevant diagnostic tests.

To report an SAE or SUSAR please complete an SAE/SUSAR CRF in as much detail as possible, and ensure that the PI or delegate has reviewed the event for causality and expectedness, and has signed the form.

All SAEs and SUSARs will be reviewed by the CI, or designated representative, to confirm causality and expectedness. In the event of a SUSAR, the CTRU will notify the Medicines and Healthcare products Regulatory Agency (MHRA), research ethics committee (REC), and Sponsors office. SUSARS will be reported to the MHRA and REC within the required expedited reporting timelines.

SAE/SUSAR CRF's should be faxed to the CTRU on 0113 343 0686

All SAEs/SUSARs will be followed-up until resolution or a final outcome has been reached. All follow-up information should be faxed/emailed to the CTRU as soon as it is available.

Please retain the original SAE/SUSAR CRF until the CTRU confirm all information is complete and any resulting queries have been resolved. At this point the original should be posted to the CTRU in real time and a copy retained in the site file.

Table 1 Summary of safety reporting requirements

Event	*Report on trial CRF*	
	Drug arms	*Non drug arms*
AE	✓	✓
AE of special interest	✓	✓
AR	✓	✕
SAE	✓	✓
SAR	✓	✕
SUSAR	✓	✕
RUSAE	✕	✓

11.4 Responsibilities

Principal Investigator:

Activities marked with an asterisk (*) must be performed by a medically-trained doctor

- Checking for AEs and ARs when participants attend for treatment / follow-up;

- Using medical judgement in assigning seriousness, causality, and expectedness using the RSI approved for the trial*;
- Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event, and providing further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting;

Ensuring that AEs and ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

CI:

- Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit;
- Using medical judgement in assigning seriousness, causality, and expectedness of SAEs where it has not been possible to obtain local medical assessment (this can be delegated to a clinical co-investigator);
- Immediate review of all SUSARs;
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan;
- Assigning Medical Dictionary for Regulatory Activities or Body System coding to all SAEs and SARs;
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

CTRU:

- Central data collection and verification of SAEs, SARs, and SUSARs according to the trial protocol onto a MACRO database;
- Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan;
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring and Ethics Committee (DMEC) and / or TSC) according to the Trial Monitoring Plan;
- Expedited reporting of SUSARs to the competent authority (MHRA in UK), main REC, and Sponsor within required timelines;
- Notifying investigators of SUSARs that occur within the trial;
- Checking for (annually) and notifying PIs of updates to the RSI for the trial;
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI, and ensuring timely submission to the MHRA and Main REC.

Trial Steering Committee:

The TSC, with an independent chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety, and consideration of new information. It will include an independent chair and not less than two other independent members. The CI

and other members of the TMG will attend the TSC meetings and present and report progress. The committee will meet annually as a minimum.

Data Monitoring and Ethics Committee:

The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment and treatment beyond the end of recruitment. The DMEC will meet or communicate via teleconference approximately annually as well as reviewing unblinded safety data at least 6-monthly. The subsequent frequency of review will be determined by the committee members. After each annual review, the DMEC will make their recommendations to the TSC about the continuation of the trial.

Trial Management Group

The TMG, comprising the CI, CTRU team, and co-investigators will be assigned responsibility for the clinical set-up, on-going management, and promotion of the trial, as well as the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion;
- CRF development;
- Obtaining approval from the main REC and supporting applications for site specific assessments;
- Completing cost estimates and project initiation;
- Appointing and facilitating the TSC and DMEC;
- Reporting of SAEs to relevant parties;
- Monitoring of screening, recruitment, treatment, and follow-up procedures;
- Auditing consent procedures, data collection, trial end-point validation, and database development.

11.5 Pregnancies

All pregnancies and suspected pregnancies in female participants should be reported to CTRU within 24 hours of the PI or designee becoming aware of the event using the pregnancy CRF and will be followed up for outcome.

11.6 Deaths

All deaths must be 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.

11.7 Overdose Definition and Reporting

11.7.1 Amitriptyline

In the event of an overdose (>**200mg** [20 tablets] ingested in one day), amitriptyline should be discontinued, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. **Additionally, in the event of**

any deliberate overdose (however small), all study medication should be stopped and the participant should be reviewed for suicidal ideation. The participant should be withdrawn from trial treatment, and assessed by the PI for consideration as to whether ongoing data collection (completion of participant questionnaires) is appropriate.

Overdose is considered an IME and should be reported as a SAE.

11.7.2 Ondansetron

In the unlikely event of overdose (>120mg ingested in one day), ondansetron should be discontinued, and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided, if clinically indicated.

If an AE(s) is associated with ("results from") the overdose, the AE(s) should be recorded as a SAE, even if no other seriousness criteria are met.

11.7.3 Loperamide

In the unlikely event of overdose (>16mg ingested in one day), loperamide should be discontinued, and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided, if clinically indicated.

If an AE(s) is associated with ("results from") the overdose, the AE(s) should be recorded as a SAE, even if no other seriousness criteria are met.

12 SAFETY MONITORING PLAN

Table 2 Safety Monitoring Plan

Risks associated with trial interventions ☐ **LOW ≡** Comparable to the risk of standard medical care ☒ **MODERATE ≡** Somewhat higher than the risk of standard medical care ☐ **HIGH ≡** Markedly higher than the risk of standard medical care	
Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):* The known risks and benefits to participants are well studied and available in the relevant SPCs. Although this protocol will study the use of these drugs outside of their licensed indications there is no reason to believe that the risk in terms of AEs will be any higher in this population. These drugs will also be used in much lower doses than are often prescribed, decreasing the risk of side effects occurring.	

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?	
IMP	**Body system/Hazard**	**Activity**	**Frequency**
Amitriptyline, loperamide and ondansetron	**Contraindications to IMP**	All study medications have a number of contraindications listed in the SPCs. Participants with these contraindications will be excluded from trial entry through the eligibility criteria/screening process.	Eligibility assessment
	Interaction	All study medications have a number of interactions listed in the SPCs. Clinicians are advised to consider interactions prior to trial entry. Participants will be asked to inform the research nurse if they begin any new treatments whilst on the study.	Eligibility assessment
	Pregnancy	The SPCs for amitriptyline and ondansetron state that pregnancy is not recommended, The SPC for loperamide states that pregnancy is not advisable. Therefore patients who are pregnant, or planning to get pregnant, are excluded from the study and a pregnancy test will be administered to all women of child-bearing potential prior to study entry. This is over and above standard of care where pregnancy testing is not performed as the risks associated with these medications, and the doses used in this study, are considered low (see appendix 1 for further information). Patients will be advised not to become pregnant during the course of the trial and to advise the study team if they think they are pregnant.	Eligibility assessment
	Compliance with treatment (medication will be taken by	Participants will be given instructions to take home to provide details of how each treatment should be taken.	Throughout treatment

	participants at home)		Prior to entering the trial and before the start of treatment
		Participants will receive telephone calls from research nurses to support dose titration and will have an optional review with a clinician at 4 weeks to discuss any concerns. Participants will also be given a diary card to record the number of tablets they have taken each day.	Throughout treatment
	Allergic reaction	Participants with known allergies to amitriptyline, loperamide, and ondansetron will be excluded from the trial.	Eligibility assessment
Amitriptyline	**Deliberate overdose/suicide attempt**	Participants will be screened for suicidal ideation at screening and at baseline. We will also have a protocol in place to guide study nurses to notify the patient's GP in order to request urgent review (or other appropriate steps), in the event that someone with active suicidal ideation is identified, either at initial screening, or later interim screening checks, and prior to dispensing any drug prescriptions. We are prescribing a very low daily dose, and the sequential dispensing means that participants will only have a very limited total amount of drug that they can access. Patients already currently prescribed a TCA for the treatment of depression will be excluded.	Eligibility assessment and at baseline prior to randomisation
Loperamide	**Toxic megacolon**	During eligibility screening the blood and stool sample tests will confirm that there is no active inflammation present in the colon. In the event of clinical uncertainty regarding the stability of the patient's UC, a flexible	Eligibility assessment and throughout

		sigmoidoscopy may be performed at the discretion of the treating physician. In this situation, an endoscopic mayo score of ≤1 at flexible sigmoidoscopy will confirm the patient's eligibility for inclusion into the trial. Participants will be informed about the risks of developing toxic megacolon and will be given instructions on what to do if they begin to develop symptoms. Constipation is being monitored as an AE of special interest.	treatment

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. IDMC, independent data review,...)

A DMEC will be convened for the trial, who will meet on an annual basis and will review interim unblinded safety information for the trial, as agreed by the committee at their initial meeting. Safety information will be reviewed at least 6-monthly whilst participants remain on treatment. Full interim reports will be presented to the DMEC, in confidence, annually. The DMEC will, in light of these reports, have the authority to recommend trial closure to the TSC should they have concerns over the safety or ethics of the trial. The TSC have the authority to recommend appropriate action including amendments to, or closure of, the trial at any time.

Participant data will be entered on to a validated database and monitored for completeness and quality by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. Validation checks will be incorporated into the trial database to verify the data, and discrepancy reports will be generated for resolution by the trial site. Priority validations will be incorporated to ensure that any discrepancies related to participant rights, or the safety of participants, are expedited to sites for resolution.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size and Power Considerations

13.1.1 Phase 2

In the phase 2 period of the trial, a total of 396 participants will be recruited, 66 participants per intervention arm and 132 to the control group. This provides 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, [26] with a 1-sided 20% significance level, assuming 10% of participants are lost to follow-up.

An absolute difference of 17% equates to a number needed to treat of 6. The IBS literature demonstrates consistently that therapies with a number needed to treat around this level are usually taken up in clinical practice, whereas there is often less enthusiasm for those with more modest effectiveness and a higher number needed to treat. This is a similar minimum clinically important difference to that we have stipulated in a trial in IBS, the EME-funded TRITON trial of ondansetron (15/74/01).

It is recommended that in a trial comparing one control group to several intervention arms, allocation should be in the ratio 1 to each intervention arm and the square root of the number of intervention arms to the control group, in order to maximise efficiency (smallest sample size for a given power). [35] In this case the ratio is 1:1:1:1:2.

13.1.2 Phase 3

If two interventions are carried forward from phase 2, a total of 491 participants are required: an additional 38 participants per intervention arm, and a further 19 participants in the control group (ratio 2:2:1). This will provide 90% power to detect a 16-point difference in the IBD-Q at 6 months, with 2-sided 2.5% significance, assuming an extra 10% of participants are lost to follow-up, and a standard deviation (SD) of 32. [36, 37] The final allocation ratio is 5:5:7 across both phases.

If only one intervention is carried forward from phase 2, a total of 426 participants are required: an extra 20 participants recruited to that intervention arm, and an extra 10 participants recruited to the control group (ratio 2:1). Again, this gives 90% power to detect a 16-point difference in the IBD-Q at 6 months, with 2-sided 5% significance, assuming an extra 10% lost to follow-up, and a SD of 32. [36, 37] The final allocation ratio is 5:8 across both phases.

The trial is powered to detect a 16-point difference in the IBD-Q at 6 months to assess overall clinical effectiveness. 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. [38, 39] The lowest point on this range represents the minimum clinically meaningful difference in disease specific quality of life at 6 months.

13.2 Endpoints

13.2.1 Primary Endpoint, Phase 2 - Improvement in Diarrhoea Symptoms at 8 Weeks Post-randomisation

Improvement in diarrhoea will be defined as scoring ≤2 on the diarrhoea subscale of the GSRS-IBS, [26] indicating minor discomfort from diarrhoea or less. The GSRS-IBS is a validated questionnaire, used widely in trials of medical therapies in gastrointestinal diseases. [26] 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.

13.2.2 Primary Endpoint, Phase 3 – Total IBD-Q Score at 6 Months Post-randomisation

The IBD-Q is a validated questionnaire, designed to measure disease-specific quality of life in people with inflammatory bowel disease. [27] The questionnaire has 32 items, which are grouped into four domains: bowel symptoms (10 items), systemic symptoms (five items), emotional factors (12 items), and social factors (five 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.

13.2.3 Secondary Outcome Measures (at 8 Weeks and 6 Months Post-randomisation)

13.2.3.1 Loose Stools, Diarrhoea, Urgency, and Abdominal Pain

The GSRS-IBS, [26] which is described above, will be 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.

13.2.3.2 Disease Activity (Escalation of Medical Therapy, Need for Surgery, CRP, and FC)

Data concerning need for either escalation of medical therapy for UC or surgery will be 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 will be supplemented by patient questionnaires collecting these data. Participants will also provide blood for CRP (measured in mg/L) and stool for FC (measured in mcg/g) at 6 months only, which will both be collected as continuous measures.

13.2.3.3 Mood

The HADS is a well-validated, commonly used, self-report instrument for detecting anxiety and depression in people with medical illnesses. [28] It consists of a total of seven items measuring anxiety, and seven measuring depression, scored from 0 to 3, with a total score of 21 for each. Higher scores indicate more severe anxiety or depression.

13.3 Data Analysis

13.3.1 General Considerations

Statistical analysis is the responsibility of the CTRU statistician. The detailed statistical analysis plan (SAP) will be written in accordance with current CTRU standard operating procedures. It will be will be finalised and agreed by appropriate members of the trial team (trial and supervising statistician, the CI, the CTRU lead methodologist, project delivery lead, trial manager) before any analyses are undertaken. Any changes to the final analysis plan and reasons for change will be documented. Any deviation(s) from the final statistical plan in the final analysis will be described, and justification given, in the final report.

Analysis will take place in three stages, for the internal pilot, the phase 2 period, and the phase 3 period. The second of these is a formal interim analysis at which effectiveness on a single outcome (improvement in diarrhoea) will be analysed to determine which of the treatment groups will be carried forward into the phase 3 period of the trial.

13.3.2 Timing of Analyses

The recruitment progression criterion in the internal pilot will be assessed after 6 months of recruitment; rates of treatment withdrawal, adherence to a low FODMAP diet, and follow-up will be assessed after 12 months of recruitment.

The interim analysis of diarrhoea responders, to determine which treatments are carried through to the phase 3 period, will occur when all participants recruited during the phase 2 period have completed their 8-week follow-up data.

The final analysis will take place when all participants in the remaining treatment arms complete follow-up at 6 months, and after the database has been cleaned and locked.

13.3.3 Analysis Populations

Analyses will be on the ITT population, which will include all randomised participants, analysed according to the study arm to which they were randomised, irrespective of adherence to treatment. A per protocol analysis of the primary outcome will also be conducted, based on pre-defined criteria associated with intervention adherence.

13.3.4 Analysis of Internal Pilot

Data from the internal pilot will be analysed initially using descriptive statistics to evaluate the progression criteria. Outcome data from participants in the internal pilot will be included in the main trial analyses.

13.3.5 Descriptive Statistics

Descriptive statistics will be presented for demographics and baseline data, endpoints, and safety data. Continuous variables will be summarised by mean, SD, median, minimum, and maximum, as well as interquartile range, if appropriate. Categorical variables will be summarised by frequencies and percentages. A CONSORT diagram will display the flow of participants through the trial. Baseline characteristics of those lost to follow-up will be compared with those not lost to follow-up to assess for bias, and to inform the methods for handling missing data in inferential analyses.

13.3.6 Phase 2 Analysis and Progression to Phase 3

At the end of the phase 2 period, the diarrhoea responder rates at 8 weeks will be compared between the control group and each of the intervention arms individually, in logistic regression models adjusted for the stratification factors. Results will be expressed as odds ratios, together with 80% confidence intervals and p-values. Intervention arms will only be carried forward to phase 3 if the p-value in comparison with the control group is <0.2. This will correspond to an odds ratio >2, or to an absolute difference in response rate of 17%, when compared with the control group, if the response rate in the control group is 33%. If more than two intervention arms achieve this difference, the observed response rates, as well as safety, will be taken into account to decide which treatment arms should progress.

13.3.7 Primary Endpoint Analysis

The primary analysis in the phase 3 period will compare IBD-Q scores at 6 months between the control group and the intervention arms individually, in linear regression models adjusted for the stratification variables and baseline IBD-Q. Results will be expressed as point estimates, together with 95% or 97.5% confidence intervals (when there are one or two intervention arms, respectively), and p-values.

For the primary endpoints only, missing data will be multiply imputed, where appropriate. When questionnaires have missing items, scoring instructions specific to the questionnaires will be followed, or if no such instructions exist the summary scores will be calculated from the non-missing items, as long as at least half are non-missing.

Sensitivity analyses on a per-protocol population will test the robustness of the results.

13.3.8 Secondary Endpoint Analysis

Secondary continuous endpoints (IBD-Q at 8 weeks, GSRS-IBS,HADS anxiety and depression scores, CRP, FC and constipation) will be analysed in the same manner as the primary endpoint, with the endpoint in question at baseline replacing the IBD-Q at baseline in the model. Secondary binary endpoints will be analysed similarly in logistic regression models. Other secondary endpoints pertaining to disease activity and tolerability (Escalation of Medical Therapy, Need for Surgery, and flares of disease activity)

An exploratory moderator analyses will be conducted to investigate if treatment effect varies by diarrhoea severity, disease extent, or mood at baseline, by testing the interaction between such effects and the treatment allocation. Similarly, the number of contacts or mood during follow-up will be tested to see if this mediates patient outcomes.

13.3.9 Safety Analyses

Routine collection of all AEs and ARs will not take place, due to the well-established safety profile of the study drugs. Rates of constipation and flares of disease activity will be of particular interest. Flares of disease activity will be treated as an AE of special interest and reported on a Flare CRF. Rates of constipation will be collected by participants self-report at week 8 and month 6. Other endpoints related to disease activity (Escalation of Medical

Therapy, Need for Surgery, CRP, and FC) will also be summarised as descriptive statistics and presented by arm

Responsible gastroenterologists will be encouraged to report AEs of special interest and SAEs to the trial team. All AEs, SAEs, and SUSARs will be reported to the DMEC within the relevant time frames, and appropriate action will be taken. Any reported form of self-harm, or suicide will be treated as an IME, whether or not related to taking the trial medication, and reported on an SAE form. Descriptive statistics for all safety data will be summarised by arm.

13.3.10 Adherence

Adherence at 8 weeks and 6 months in the IMP arms is measured by a 4-point-Likert scale.

Adherence will also be assessed via a summary question at 8 weeks and 6 months. For the Amitriptyline arm, the question will be as follows:

““Since you were last asked, which of the options best describes how often you have taken at least one tablet of the trial medication daily?”
A. Every day or nearly every day
B. Half of the days or more than half of the days
C. Less than half of the days
D. None or nearly none of the days”

For the Ondansetron and Loperamide arms, the summary question at 8 weeks and 6 months will be as follows:

““Since you were last asked, which of the options best describes how often you have taken at least one tablet of the trial medication weekly?”
A. Every week or nearly every week
B. Half of the weeks or more than half of the weeks
C. Less than half of the weeks
D. None or nearly none of the weeks”

Descriptive statistics, by arm, will be summarised to show the number of adherent patients at each time point, for both of the methods described above.
For those randomised to a low FODMAP diet, adherence at 8 weeks and 6 months will be determined using a 4-point-Likert scale [33]. The question and responses will be as follows:

“Which of the following best describes your adherence to the Low FODMAP diet?”
A. Continued strict low-FODMAP diet
B. Reintroduced high-FODMAP foods to tolerance
C. Continued low-FODMAP diet 50% of the time
D. Returned to habitual diet

Descriptive statistics will be summarised and presented alongside results of the adherence summary question in the IMP arms, as described above.

FODMAP content will be assessed at 8 weeks and 6 months via the CNAQ [34] in all participants, in order to verify that the FODMAP content is less in the low FODMAP diet arm at follow-up, compared with the other four trial arms. Descriptive statistics only will be presented for the FODMAP content, which will be displayed by arm.

The CNAQ is a semi-quantitative food frequency questionnaire validated to assess FODMAP and nutrient intake, and is determined using an online automated entry system.

14 MONITORING, AUDIT AND INSPECTION

14.1 Monitoring

Trial supervision will be established according to the principles of GCP and in-line with UK Policy Framework for Health and Social Care Research. This will include establishment of a core project team, TMG, an independent TSC, and an independent DMEC. A trial monitoring plan will be developed and will be informed by a trial risk assessment, which will consider the safety or physical or mental integrity of the trial participants and the scientific value of the research. This trial monitoring plan will detail the timing and content of reports to monitor trial conduct, implementation, and adherence with the Consolidated Standards of Reporting Trials (CONSORT). Procedures will be in place to assess risk on an ongoing basis, with adjustments made accordingly.

14.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, confirmed as not available, or the trial is at analysis.

The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

14.3 Clinical Governance Issues

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 will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts/Health Boards.

15 ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be 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. Written, informed consent will be obtained from the participants prior to registration into the study. The right of a participant to refuse participation without

giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons, and without prejudicing his/her further treatment. The study will be submitted to, and approved by, a main REC and the appropriate Site Specific Assessor for each participating centre prior to entering participants into the study. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms, and all other relevant study documentation.

Ethical and Regulatory Approvals for the Conduct of Study

Initial Approval

The trial will be submitted to and approved by a REC, the MHRA, and the Health Research Authority (HRA). The study documents will also be sent to local Research and Development/Innovation departments for each participating site prior to the start of recruitment at site. The CTRU will provide a copy of the final protocol, patient information sheets, consent forms, and all other relevant trial documentation that will be used.

Amendments

Proposed amendments to the protocol and study documents will be submitted for ethical, HRA and, where relevant, regulatory approval by the CTRU, once Sponsor and funder review has been obtained. Amendments requiring approval are to be implemented only after a copy of the approval letter has been obtained.

Urgent safety measures, which result in a substantial trial amendment, may be implemented prior to receiving Sponsor or ethical/regulatory approval. However, approval will be obtained as soon as possible after implementation.

SUSAR Reports, Annual Safety Reports, and End of Trial Notification

The main REC/MHRA will be sent all SUSAR reports and annual safety updates in order to facilitate their continuing review of the study, and will also be informed about the end of the trial, within the required timelines.

Protocol Compliance

Protocol compliance will be assessed throughout the study. Protocol deviations, unplanned non-compliance, or breaches are considered departures from the approved protocol.

Frequently re-occurring deviations are not acceptable and could, potentially, be classified as a serious breach. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on clinical trials.

Protocol violations should be reported immediately to the CTRU using the protocol violations CRF.

Protocol violations that need to be reported include:

- Breaches of the eligibility criteria;
- Drug administration errors related to the study drugs which lead to an SAE (note that other drug administration errors, that do not lead to an SAE, may also constitute a violation)
- Overdose.

If the protocol violation is also associated with an event that meets the criteria of an SAE or SUSAR this should also be reported in accordance with the pharmacovigilance section of the protocol.

16 QUALITY ASSURANCE

16.1 Quality Assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the NHS RGF (and Scottish Executive Health Department RGF for Health and Social Care 2006 for studies conducted in Scotland), and through adherence to CTRU standard operating procedures (SOPs).

16.2 Serious Breaches of GCP or Trial Protocol

The CTRU and the Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators will promptly notify the CTRU of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. A “serious breach” is a breach which is likely to effect to a significant degree:

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

Sites should contact the CTRU trial co-ordinators for further information.

16.3 Insurance and Indemnity

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

17 CONFIDENTIALITY

Confidentiality and Data Protection

All information collected during the course of the main trial will be kept strictly confidential. Information will be held securely on paper at the CTRU. In addition, the CTRU will hold electronic information on all trial participants. The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

Precautions will be taken to ensure that patient confidentiality is preserved at all times. The patient consent form will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

The trial staff at participating sites will be responsible for ensuring that any data/documentation sent to the CTRU is appropriately anonymised, as per instructions given by CTRU in accordance with the trial procedures, to conform to the 2018 Data Protection Act.

The CTRU will comply with all aspects of the UK 2018 Data Protection Act. Operationally this will include:

- Explicit written consent from participants to record personal details including name, date of birth, and NHS number;

- Appropriate storage, restricted access, and disposal arrangements for patient's personal and clinical details;

- Consent from participants for access to their medical records by responsible individuals from the research staff, or from regulatory authorities, where it is relevant to trial participation;

- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research;

- Copies of participants consent forms, which will include patient's names, will be collected when a patient is randomised into the trial by the CTRU. In addition patient name and email address will be collected for questionnaire posting. All other data collection forms that are transferred to, or from, the CTRU will be coded with a unique patient trial number and will include two patient identifiers, usually the patient's initials and date of birth;

- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participants name must be redacted by site before sending;

- Where anonymisation of documentation is required, research sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a patient withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

18 TRIAL OPERATIONAL STRUCTURE

Chief Investigator
The CI is involved in the design, conduct, co-ordination, and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, the investigational drug supply, and pharmacovigilance within the trial.

Sponsor
The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the Delegation of Duties.

Clinical Trials Research Unit
The CTRU at the University of Leeds will have responsibility for the conduct of the trial, in accordance with the NHS RGF and CTRU and Sponsor SOPs, as per the delegation of duties. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP conditions and principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule, and statistical analysis and reporting for the trial. In addition the CTRU will support main REC, NHS permissions submissions and clinical set-up, ongoing management including training, monitoring reports, and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, and all statistical analyses.

Pharmacy/Grant Holder/Collaborators for Sub Studies

Yvonne McKenzie is a co-applicant and a specialist in delivery of the low FODMAP diet and will assume the role of Lead Dietitian. The role of the Lead Dietitian is to provide expertise and training to research sites, either at a face-to-face visit or remotely, in delivery of the low FODMAP diet within the MODULATE trial. Additionally, the Lead Dietitian will be the primary contact for trial dietitians across all sites to provide advice and support for this intervention throughout the duration of the trial. As a co-applicant of the trial, the Lead Dietitian is required to attend TMG meetings to aid decisions in coordination and conduct of the trial. The Lead Dietitian may also be required to participate in analysis and write-up of the study results prior to publication.

19 STATEMENT OF INDEMNITY

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

20 OVERSIGHT/TRIAL MONITORING GROUPS COMMITTEES

Trial Management Group
A TMG will be convened including the CI, co-investigators, and identified key collaborators, the trial statistician, and trial manager. PIs and key study personnel may be invited to join the TMG, as appropriate, to ensure representation from a range of sites and professional groups. Notwithstanding the legal obligations of the Sponsor and CI, the TMG will have operational responsibility for the conduct of the trial.

The TMG terms of reference (ToR) will define the membership, roles, and responsibilities of the TMG, each member of the committee will be required to confirm participation on the committee under the ToR. The TMG will meet monthly. Specifically the TMG will be responsible for: protocol completion, CRF development, obtaining approval from the main REC, HRA and supporting applications for local approvals, submitting a CTA application and obtaining approval from the MHRA, completing cost estimates and project initiation, nominating members and facilitating the TSC and DMEC, monitoring of screening, recruitment, treatment and follow-up procedures, monitoring consent procedures, data collection, and trial end-point validation.

Data Monitoring Ethics Committee
A DMEC will be convened to monitor data collected during the study, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue. It will consist of an independent chair, an independent statistician, and an independent clinician.

The DMEC ToR will define the membership, roles, and responsibilities of the DMEC. Each member of the DMEC will be required to confirm participation on the committee under the ToR. The DMEC will meet annually as a minimum.

Trial Steering Committee
A TSC will be convened with an independent majority. Participation will include, as a minimum, an independent chair, an independent statistician, an independent clinician, a PPI representative, the CI, the Sponsor's representative, and other members of the TMG as required to update on trial progress. The role of the TSC will be to provide overall supervision of the trial progress and, as necessary, advice to the TMG on operational issues. The TSC will meet annually as a minimum.

The TSC ToR will define the membership, roles, and responsibilities of the TSC. Each member of the TSC will be required to confirm participation on the committee under the ToR.

Public Advisory Group/Patient and Public Involvement (PPI)
The PPI group will be convened to work with the CI to:

- Ensure the trial is carried out in an ethical and respectful way;
- Limit participant burden;
- Maximise recruitment;

- Ensure that the patient perspective is central to decision-making throughout study management;
- Ensure effective, clear communication with participants and the public;
- Anticipate issues that may influence subsequent uptake of any of the interventions should the trial demonstrate effectiveness.

The PPI lead will also be an active member of the TMG, and another patient representative from the advisory group will sit on the TSC. Roles and responsibilities are described in the corresponding ToR.

21 FUNDING

This project is funded by the National Institute for Health Research. (NIHR) Health Technology Assessment (HTA) Programme (Grant Ref: 17/33/03)

22 PUBLICATION POLICY AND DATA DISCLOSURE

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contribution. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data;

- Substantial contribution to drafting the article or revising it critically for important intellectual content;

- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publications, subject to journal authorship restrictions. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting, and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the phase III primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators

must not publish data concerning their participants that is directly relevant to the questions posed in the trial, until the first publication of the analysis of the primary endpoint.

23 REFERENCES

1. Timmer, A., et al., *Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis.* Cochrane Database Syst Rev, 2016. **May 18;(5):CD000478**.
2. Wang, Y., et al., *Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis.* Cochrane Database Syst Rev, 2016. **Apr 21;(4):CD000543**.
3. Wang, Y., et al., *Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis.* Cochrane Database Syst Rev, 2016. **May 9;(5):CD000544**.
4. Gracie, D.J., et al., *Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease.* Am J Gastroenterol, 2016. **111**: p. 541-51.
5. Gracie, D.J., et al., *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**: p. 376-384.e5.
6. Gracie, D.J. and A.C. Ford, *Ongoing symptoms in ulcerative colitis patients in remission: Irritable bowel syndrome or gastrointestinal symptoms in the absence of inflammation?* Inflamm Bowel Dis, 2017. **23**: p. E4-e5.
7. Williams, C.J., L. Peyrin-Biroulet, and A.C. Ford, *Systematic review with meta-analysis: Malignancies with anti-tumour necrosis factor-alpha therapy in inflammatory bowel disease.* Aliment Pharmacol Ther, 2014. **39**: p. 447-58.
8. Ford, A.C. and L. Peyrin-Biroulet, *Opportunistic infections with anti-tumor necrosis factor-a therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials.* Am J Gastroenterol, 2013. **108**: p. 1268-1276.
9. Lichtenstein, G.R., 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**: p. 1051-1063.
10. Beaugerie, L., et al., *Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study.* Lancet, 2009. **374**: p. 1617-1625.
11. Hookway, C., et al., *Irritable bowel syndrome in adults in primary care: Summary of updated NICE guidance.* BMJ, 2015. **350**: p. h701.
12. Garsed, K., et al., *A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea.* Gut, 2014. **63**: p. 1617-25.
13. Ford, A.C., et al., *Effect of antidepressants and psychological therapies in irritable bowel syndrome: An updated systematic review and meta-analysis.* Am J Gastroenterol, 2019. **114**: p. 21-39.
14. Ruepert, L., et al., *Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome.* Cochrane Database Syst Rev, 2011. **Aug 10;(8):CD003460**.
15. Ford, A.C., et al., *American College of Gastroenterology monograph on management of irritable bowel syndrome.* Am J Gastroenterol, 2018. **113 (Suppl 2)**: p. 1-18.

16. Gorard, D.A., G.W. Libby, and M.J. Farthing, *Influence of antidepressants on whole gut orocaecal transit times in health and irritable bowel syndrome.* Aliment Pharmacol Ther, 1994. **8**: p. 159-166.

17. Talley, N.J., et al., *GR 38032F (ondansetron), a selective 5HT3 receptor antagonist, slows colonic transit in healthy man.* Dig Dis Sci, 1990. **35**: p. 477-80.

18. Sun, W.M., N.W. Read, and M. Verlinden, *Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence.* Scand J Gastroenterol, 1997. **32**: p. 34-8.

19. Pedersen, N., et al., *Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease.* World J Gastroenterol, 2017. **23**: p. 3356-3366.

20. Macer, B.J., S.L. Prady, and A. Mikocka-Walus, *Antidepressants in inflammatory bowel disease: A systematic review.* Inflamm Bowel Dis, 2017. **23**: p. 534-550.

21. Mikocka-Walus, A., 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**: p. 509-514.

22. Mowat, C., et al., *Guidelines for the management of inflammatory bowel disease in adults.* Gut, 2011. **60**: p. 571-607.

23. Excellence, N.I.f.H.a.C., *Ulcerative colitis: Management in adults, children and young people.* https://www.nice.org.uk/guidance/cg166/evidence/full-guideline-pdf-190220365, 2013.

24. Derwa, Y., et al., *Systematic review with meta-analysis: The efficacy of probiotics in inflammatory bowel disease.* Aliment Pharmacol Ther, 2017. **46**: p. 389-400.

25. Gracie, D.J., et al., *Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: A systematic review and meta-analysis.* Lancet Gastroenterol Hepatol, 2017. **2**: p. 189-199.

26. Svedlund, J., I. Sjodin, and G. Dotevall, *GSRS - a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease.* Dig Dis Sci, 1988. **33**: p. 129-134.

27. Guyatt, G., et al., *A new measure of health status for clinical trials in inflammatory bowel disease.* Gastroenterology, 1989. **96**: p. 804-10.

28. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**: p. 361-370.

29. Rogler, G., 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**: p. 670-7.

30. Cairns, S.R., et al., *Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002).* Gut, 2010. **59**: p. 666-689.

31. Murray, K., 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**: p. 110-9.

32. Major, G., et al., *Colon hypersensitivity to distension, rather than excessive gas production, produces carbohydrate-related symptoms in individuals with irritable bowel syndrome.* Gastroenterology, 2017. **152**: p. 124-133.e2.

33. O'Keeffe, M., 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. **doi: 10.1111/nmo.13154**.

34. Barrett, J.S. and P.R. Gibson, *Development and validation of a comprehensive semi-quantitative food frequency questionnaire that includes FODMAP intake and glycemic index.* J Am Diet Assoc, 2010. **110**: p. 1469-76.

35. Julious, S.A., *Seven useful designs.* Pharm Stat, 2012. **11**: p. 24-31.

36. Probert, C.J., et al., *Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial.* Gut, 2003. **52**: p. 998-1002.

37. Higgins, P.D., et al., *Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis.* Gut, 2005. **54**: p. 782-8.

38. Feagan, B.G., et al., *The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients.* Am J Gastroenterol, 2007. **102**: p. 794-802.

39. Irvine, E.J., 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**: p. 287-96.

24 APPENDICES

Appendix 1. Pregnancy Testing

The SPC states that amitriptyline is not recommended in pregnancy, unless clearly necessary, and only after careful consideration of the risk/benefit. NICE guidance recommends the use of TCAs such as amitriptyline for the second-line treatment of IBS, which is at a much lower dose (10 – 30 mg) than it is licenced for in depression (150 mg – 200 mg). In normal practice, patients do not undertake pregnancy testing prior to commencing low dose amitriptyline for treatment of IBS, nor do they undertake pregnancy. Furthermore, amitriptyline has been used for many years in low doses for other conditions, including the treatment of chronic painful conditions, without the need for pregnancy testing.

The MHRA released a Drug Safety Update in January 2020 relating to the use of Ondansetron during the first trimester of pregnancy. This is reflected in the current SPC (26-Nov-2019) and warns against the use of Ondansetron in the first 12 weeks of pregnancy due to the slight increased risk of orofacial malformations based on human experience in epidemiological studies.

Pregnancy is an exclusion criteria in this study: any woman who is pregnant, or is planning to become pregnant during the time period covered by the trial, will be refused entry into the trial. All women of childbearing potential (defined as women who have had any menstrual bleeding

in the last 12 months and who are not surgically sterile) must undertake a pregnancy test prior to study entry and be willing to use medically approved contraception whilst receiving treatment.

Appendix 2. Shipment of Study Medication Directly to Patients Via Royal Mail Signed For® 1st Class Delivery

Delivery of the study medication by Royal Mail Signed For® delivery directly to participant's home address under ambient shipping conditions, has been risk assessed and considered acceptable and appropriate based on the following:

- None of the IMPs used in this study are controlled drugs;
- Amitriptyline is widely prescribed in primary care with over 50 years of use data. It is being used at a low dose (10mg rather than 75mg tablets).
- Ondansetron has been widely used for nearly three decades and at the doses used in this study has shown to be extremely safe.
- Loperamide is available over the counter to buy and known to be extremely safe.
- All three drugs are stable with a good margin of safety and a long shelf life. Study medication will be re-packaged to ensure it is protected from light and moisture.
- The IMPs will be dispensed by the site pharmacy as per local practice and posted to the patient under ambient shipping conditions. This is similar to clinical practice and standard care where a patient would take the medication home with them in ambient conditions once it has been dispensed.
- Recorded delivery must be used to ensure the intended recipient receives the medication and to prevent an unintended person picking up study medication that has been posted through the door. Participants will confirm receipt of the medication. In the event that they do not receive the medication, central pharmacy will keep a log of the tracking numbers so that the parcel can be traced.
- Low dose (10mg) amitriptyline is being sent, using small quantities while at the same time keeping the study logistically possible. Therefore in the unlikely event that the medication is received by an unintended recipient, the amount they have access to has been limited.

Appendix 4. TIDieR

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Nº	What	Details
1	**Name**	Low FODMAP diet
2	**Why: Rationale, theory, goals**	FODMAP is an acronym for "fermentable oligo-, di-, and mono-saccharides and polyols". 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. Most FODMAPs occur naturally in foods within the human diet. However, polyols can be added artificially during the commercial production of foods and drinks. Participants randomised onto the low FODMAP diet arm of the study will be instructed to restrict intake of fructans, galacto- ligosaccharides, polyols, lactose, and fructose (high levels, or where fructose is in excess of glucose) until the end of week 8. This restriction process will be guided by counselling from a specialist gastroenterology dietitian, who has adequate experience in treating patients with IBS-like symptoms on the low FODMAP diet. If participants see an improvement in their symptoms after 8 weeks they will continue onto FODMAP reintroduction. During this stage, participants will reintroduce FODMAP sub groups separately whilst maintaining an otherwise low FODMAP diet.

		After reintroduction, the dietitian can then interpret the participant's specific FODMAP triggers and work towards establishing a long-term personalised FODMAP diet. This involves fully re introducing FODMAPs that are tolerated well, and only restricting foods that triggered symptoms.
3	**What Materials**	**Dietitian Appointment 1** In the first face-to-face visit with the dietitian, two written comprehensive educational booklets(copyright Guy's and St Thomas' NHS Foundation Trust and King's College London) will be used, which will be given to each participant to take home. The booklets are titled 'Suitable products for the low FODMAP diet' and 'Reducing fermentable carbohydrates the low FODMAP way'. These booklets contain photographs, explanations of the rationale behind the low FODMAP diet, and lists of foods that are suitable to consume, along with foods that should be avoided. The booklets also contain recipe suggestions and information about a mobile application that participants can choose to download to help them identify which foods are suitable. **Dietitian Appointment 2** After 8 weeks on the low FODMAP diet (the restriction stage), each participant will attend a second face-to-face 30-minute session. At this visit, each participant will be provided with a further written resource to use, and will note their results of reintroducing individual high FODMAP foods over a 3-day challenge. This booklet is titled 'Reintroducing FODMAPs and long-term self-management' (copyright Guy's and St Thomas' NHS Foundation Trust and King's College London) and contains information on how to reintroduce each FODMAP group, tips for long-term self-management and how to follow a long-term personalisation of the low FODMAP diet.
4	**What Procedures**	• The intervention will last for 6 months and includes three face-to-face visits with a dietitian and one telephone call. • The core constituents of the low FODMAP diet intervention are guided dietary counselling, whilst informing participants of which foods may be triggering their symptoms, and then how to restrict and replace them whilst maintaining a balanced diet.

		• The low FODMAP diet is divided into three stages (restriction, reintroduction, and personalisation) to reflect the progression of participants. The diet is guided by the site dietitian but can be undertaken at home. • Intervention delivery is initiated by the low FODMAP trained dietitian who will arrange an appointment with the participant post-randomisation. • Dietitian appointment 1 (week 1), appointment 2 (week 8), and appointment 3 (month 6) are face-to-face, on-site appointments. • The review at week 16 is a telephone call.
5	**Who provided**	• Sites will be selected where all dietitians on site are supportive of the study, and where key staff who are identified as being able to support the low FODMAP intervention are experienced in delivering the diet to patients with IBS like symptoms. • Yvonne McKenzie (study dietitian) will visit each centre prior to commencement of recruitment, in order to discuss the study protocol with the local dietitian, and cover study practicalities. • Intervention training at this visit will include an explanation of the roles of site research staff, the resources to be used in intervention delivery, and any additional research tasks that on site dietitians will be expected to complete. • Supervision of dietetic staff will be by usual NHS line management. • There will be ongoing support provided throughout the trial, which will include telephone calls, central teleconferences of all local dietitians, and further site visits if needed.
6	**How: mechanisms of delivery**	• The intervention will include a minimum of two face-to-face visits and one telephone call with the site dietitian. • Each participant will be seen individually. • The participants may not see the same dietitian at each visit, depending on the capacity of the site dietitians.
7	**Where: location of delivery**	The dietitian sessions will take place at each site's usual outpatient dietetic clinic room setting. Education, resources and support given to each participant should help them to incorporate the low FODMAP restriction into their daily activities at home.

8	**When and how much**	• The low FODMAP diet is delivered over a 6-month schedule involving three stages: restriction; reintroduction, and personalisation. • The intervention will include a minimum of two face-to-face visits and one telephone call with the site dietitian. • For 8 weeks participants will restrict high FODMAP foods from their diet. At the second face-to-face appointment adherence and responsiveness to the diet will be assessed, as per the protocol. • As participants progress to the reintroduction phase they will then reintroduce groups of FODMAPs and monitor their effect on symptoms.
9	**Tailoring**	• All participants will attend the first and second face-to-face appointments. • At the second face-to-face appointment, the dietitian will decide whether the patient has responded positively to the intervention, by assessing adherence to the low FODMAP diet and whether overall gastrointestinal symptoms have improved. • Those who do not respond or adhere to the low FODMAP diet will return to their usual diet and will be advised to return for a final data collection visit at 6 months with the research nurse. • Those who respond to the low FODMAP dietary intervention will progress to the next stage of the diet, the reintroduction stage, and will receive an additional telephone call at 16 weeks and will attend a appointment with both the dietitian and research nurse present at 6 months.
10	**Modifications**	N/A
11	**How well (planned)**	• Intervention fidelity will be monitored using a bespoke fidelity check list. • This check list covers three domains of setting, knowledge of content, and competency of delivery. This check list will be self-completed by dietitians at all visits, with a random sample of ~10% being assessed to ensure consistency and competency across sites.

Appendix 5 Schedule of Events

Screening - Randomisation

TIMEPOINT	Screening			Baseline	
ASSESSMENTS	Pre-screening Call	Consent Visit	Screening	Baseline	
Verbal consent and preliminary evaluation of inlcusion/ exclusion criteria	x				
Suicidal ideation	x			x	
Duration and extent of UC	x				
Written informed consent [1]		x			
Registration		x			
Medical history and medications			x		
tTG			x		
FC, CRP [2,3]			x		
Flexible sigmoidoscopy [4]			x		
Pregnancy test [5]			x		
Confirm eligibility.				x	
GSRS	x			x	
IBD-Q				x	
CNAQ				x	
HADS				x	
Sociodemographic details, current meds, duration and extent of UC, previous or current psychiatric diagnoses				x	

RANDOMISATION

1 Written Informed Consent must be obtained before blood test is carried out.

2 FC/CRP levels to be assessed within 4 weeks prior to randomisation.

3 If CRP result is abnormal, which may be a temporary abnormality, the blood test may be repeated approximately 1-2 weeks later if the participant wishes to undertake further screening for the study.

4 If required due to clinical uncertainty of UC stability or in the presence of rectal bleeding.

5 For women of child bearing potential. If hospital screening visit is >7 days prior to randomisation, a home pregnancy test must be taken before a participant can be randomised.

Control group

TIMEPOINT	RANDOMISATION	Week 8		Month 6
ASSESSMENTS		Patient complete	Nurse complete	Final visit
FC, CRP				x
Concomitant medication check				
GSRS		x		X
IBD-Q		x		x
CNAQ		x		
HADS		x		x
Loperamide usage		x		x
Need for either escalation of medical therapy for UC or surgery;		x	x	x
SAE/SAR/SUSAR check			x	x
Check for flare of disease activity			x	x

Amitriptyline

TIMEPOINT		Week 1	Week 3	Week 4	Week 8		Month 3	Month 6
ASSESSMENTS		Phone call	Phone call	Clinician review[1]	Patient complete	Nurse complete	Phone call	Final visit
Suicidal ideation	RANDOMISATION		X				X	
FC, CRP								X
Concomitant medication check		X	X			X	X	X
GSRS					X			X
IBD-Q					X			X
CNAQ					X			
HADS					X			X
Loperamide usage					X			X
SAE/SAR/SUSAR (toxicity) check		X	X		X	X	X	X
Need for either escalation of medical therapy for UC or surgery;					x	X		X
Adherence (via diary card)					X			X
Unused medication return								X
Study medication replenish			X				X	
Optional clinican review				X				
Contact details check		X	X				X	
Dose information		X	X				X	X
Check for flare of disease activity						X		X

1 Clinician review is optional.

Ondansetron

TIMEPOINT	RANDOMISATION	Week 1	Week 3	Week 4	Week 8		Month 3	Month 6
ASSESSMENTS		Phone call	Phone call	Clinician review[1]	Patient complete	Nurse complete	Phone call	Final visit
FC, CRP								X
Concomitant medication check		X	X			X	X	X
GSRS					X			X
IBD-Q					X			X
CNAQ					X			
HADS					X			X
Loperamide usage					X			X
SAE/SAR/SUSAR (toxicity) check		X	X		X	X	X	X
Need for either escalation of medical therapy for UC or surgery					X	X		X
Adherence (via diary card)					X			X
Unused medication return								X
Study medication replenish							X	
Optional clinican review				X				
Contact details check		X	X				X	
Dose information		X	X				X	X
Check for flare of disease activity						X		X

1 Clinician review is optional.

Loperamide

TIMEPOINT	RANDOMISATION	Week 1	Week 3	Week 4	Week 8		Month 3	Month 6
ASSESSMENTS		Phone call	Phone call	Clinician review[1]	Patient complete	Nurse complete	Phone call	Final visit
FC, CRP								X
Concomitant medication check		X	X			X	X	X
GSRS					X			X
IBD-Q					X			X
CNAQ					X			
HADS					X			X
SAE/SAR/SUSAR (toxicity) check		X	X		X	X	X	X
Need for either escalation of medical therapy for UC or surgery					X	X		X
Adherence (via diary card)					X			X
Unused medication return								X
Study medication replenish							X	
Optional clinican review				X				
Dose information[2]		X	X				X	X
Contact details check		X	X				X	
Check for flare of disease activity						X		X

1 Clinician review is optional.

2 At week 3 phone call, to collect dosing strategy information (PRN or titrated).

Low FODMAP Diet

TIMEPOINT	RANDOMISATION	Week 1	Week 8			Week 16	Month 6
ASSESSMENTS		Visit	Patient complete	Dietitian complete	Nurse complete	Phone call	Final visit
tTG							
FC, CRP							X
Concomitant medication check					X		X
GSRS			X				X
IBD-Q			X				X
CNAQ			X				X
HADS			X				X
Loperamide usage			X				X
Adverse events (check of medical notes)		X			X		X
Adverse events (self-reported questionnaire)			X				
Height/Weight		X		X			X
Dietitian counselling session		X		X		X	X
Need for either escalation of medical therapy for UC or surgery			X		X		X
Check for flare of disease activity					X		X