ISRCTN16086699 https://doi.org/10.1186/ISRCTN16086699

MODULATE: a study to evaluate the effectiveness of either amitriptyline, ondansetron, loperamide, or dietary intervention (the low FODMAP diet) against standard dietary advice for the treatment of diarrhoea in patients with stable ulcerative colitis

Submission date 13/01/2020	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data [_] Record updated in last year
Registration date 13/02/2020	**Overall study status** Stopped	
Last Edited 09/05/2025	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Ulcerative colitis (UC) is a long-term condition where the colon and rectum become inflamed. The colon is the large intestine (bowel) and the rectum is the end of the bowel where stools are stored. Small ulcers can develop on the colon's lining, and can bleed and produce pus. About 1 in 5 people with UC report ongoing diarrhoea, even when there is no sign of bowel inflammation. This also causes discomfort and distress, reducing peoples' quality of life, and impacting on their psychological health and mood.
This is a similar situation to people living with irritable bowel syndrome (IBS), who often experience troublesome diarrhoea. In IBS, a low diet low in poorly absorbed sugars (FODMAPs) improves diarrhoea, because some FODMAPs increase small intestinal water content. Drugs like ondansetron (an antisickness drug), amitriptyline (an antidepressant drug), or loperamide (an antidiarrhoeal drug) can also be effective in IBS with diarrhoea. This is because they change bowel activity, and can relieve tummy pain. These treatments may therefore help people with stable UC.

Who can participate?
People aged over 18 years with stable UC who have diarrhoea.

What does the study involve?
All participants will be provided with standard first-line dietary advice. People will also be given one of the following: a low FODMAP diet; ondansetron; amitriptyline; loperamide; or no additional treatment.

A computer will randomly decide who gets which one. People will be asked to follow the diet or take the tablets for 6 months, in addition to their doctor's usual treatment for UC. People will be aware of which treatment they get.
People will be followed up at 8 weeks and 6 months. Side effects and adherence to each treatment will be recorded as well as how many flare-ups people experience, whether usual treatment for UC has been changed, and whether surgery has been required.

What are the possible benefits and risks of participating?
Benefits- improvement in symptoms and quality of life for patients with stable UC and ongoing diarrhoea, fewer secondary care hospital visits, should help clinicians, patients and health service planners to make better-informed decisions regarding the management of diarrhoea in patients with stable UC in secondary care.
Risks- side effects associated with the drugs (although thought to be at a reduced rate due to the lower dose used).

Where is the study run from?
Leeds Institute of Medical Research at St James's University Hospital and 26 UK hospitals.

When is the study starting and how long is it expected to run for?
March 2020 to February 2023

Who is funding the study?
National Institute for Health Research (NIHR), UK

Who is the main contact?
Florence Day (public), modulate@leeds.ac.uk
Prof. Alexander Ford (scientific), a.c.ford@leeds.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-003220-21

Integrated Research Application System (IRAS)
266428

Protocol serial number
CPMS 43987, IRAS 266428

Study information

Scientific Title
Management of diarrhoea in ulcerative colitis: multi-arm multi-stage trial of low FODMAP diet, amitriptyline, ondansetron, or loperamide: MODULATE

Acronym
MODULATE

Study objectives
The use of at least one of a low FODMAP diet, amitriptyline, ondansetron, or loperamide in this group of people with UC will lead to improvements in both symptoms and quality of life, and less utilisation of secondary care health services by people with UC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 26/02/2020, Leeds West Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newscatle, NE2 4NQ, UK; +44 (0)2071048058; yorkandhumber-leedswest@nhs.net), ref: 266428
2. Approved 26/02/2020, Yorkshire and Humber- Leeds West REC (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8018; nrescommittee.yorkandhumber-leedswest@nhs.net), ref: 20/YH/0007

Study design

Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Ulcerative colitis

Interventions
The MODULATE study incorporates 5 arms, 4 interventional and 1 control. At least 2/4 interventional arms will be dropped when transitioning from a phase 2 trial to a phase 3 trial.
- The control arm consists of standard first-line dietary advice given to all patients with Irritable Bowel Syndrome (IBS).
- The first interventional arm is Amitriptyline, a tricyclic antidepressant, which at low doses is thought to slow colonic transit.
- The second interventional arm is Loperamide, an antidiarrhoeal drug also thought to slow colonic transit.
- The third interventional arm is Ondansetron, an anti-emetic thought to slow colonic transit.
- The fourth interventional arm is the Low FODMAP diet; a diet low in fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) thought to reduce bloating and painful gas within the small intestine.

For all patients randomised to an interventional arm, they will receive treatment for 6 months. All patients in the study will be asked to complete a set of questionnaires at baseline, 8 weeks and 6 months, and will visit their secondary care site at baseline and 6 months for additional investigations (following previous eligibility assessments). All participants randomised to an IMP arm will receive additional phone calls within the 6 months to collect toxicity data and for advice on dose titration. Follow-up will be completed at 6 months for all participants.

Randomisation will be performed by the University of Leeds CTRU (Clinical Trials Research Unit)' s 24-hour registration and randomisation system. Randomisation will be via minimisation at the level of the individual, stratified according to centre, degree of discomfort from diarrhoea, the extent of UC and Hospital Anxiety and Depression Scale (HADS)-Depression score.

Intervention Type
Other

Primary outcome(s)
Phase 2. Improvement in diarrhoea measured using the 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)
Phase 3. Disease-specific quality of life measured using the Inflammatory Bowel Disease Questionnaire overall score at 6 months post-randomisation (measuring bowel symptoms, systemic symptoms, emotional, and social factors)

Key secondary outcome(s))
Phase 2 and 3. Measured at both 8 weeks and 6 months:
1. Improvement in diarrhoea measured using the GSRS-IBS

2. Blood for CRP, stool for FC at 6 months only, reviewing case notes for escalation of medical therapy for UC
3. Anxiety and depression will be measured by the HADS

Completion date
28/02/2023

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/02/2024:
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 (a flexible sigmoidoscopy with a 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)
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:
9.1. Whether the patient has experienced any thoughts of harming themselves, or ending their life in the last 7-10 days?
9.2. Whether the patient currently has any thoughts of harming themselves or ending their life?
9.3. 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:
12.1. Post-menopausal (no menses for 12 months without an alternative medical cause), or;
12.2. Surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or;
12.3. Using highly effective contraception (and must agree to continue for 7 days after the last dose of the investigational medicinal product [IMP])
13. Able to complete questionnaires and trial assessments
14. Able to provide written informed consent

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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. Mayo score of < = 1 at flexible sigmoidoscopy within the past 3 months prior to initial screening telephone call
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:
9.1. Whether the patient has experienced any thoughts of harming themselves, or ending their life in the last 7-10 days?
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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 02/02/2024:
1. Inflammatory bowel disease unclassifiable or Crohn’s disease
2. Ulcerative proctitis
3. Body mass index ≤18.5 kg/m2.
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
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
8. Known allergy to TCAs, ondansetron, or loperamide.
9. Current use of a TCA at time of initial screening telephone call.
10. Previous failed treatment with 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.3
12. Contraindications to the current use of TCAs including patients with any of the following:
12.1. Taking monoamine oxidase inhibitors, or receiving them within the last 2 weeks;
12.2. Already currently prescribed a TCA for the treatment of depression
12.3 Previous myocardial infarction;
12.4. Recorded arrhythmias, particularly heart block of any degree, or prolonged Q-T interval on electrocardiogram;
12.5. Mania;
12.6. Severe liver disease;
12.7. Porphyria;
12.8. Congestive heart failure;
12.9. Coronary artery insufficiency;
12.10 Receiving concomitant drugs that prolong the QT interval (e.g. amiodarone, terfenadine, or sotalol)
13. Contraindications to the current use of ondansetron, including:
13.1. Concomitant use of apomorphine;
13.2. Concomitant use of other drugs that prolong the QT interval.
14. Contraindications to the current use of loperamide, including:
14.1. Acute UC;
14.2. Acute dysentery, which is characterised by blood in stools and high fever;
14.3. Bacterial enterocolitis caused by invasive organisms;
14.4. Pseudomembranous colitis associated with the use of broad-spectrum antibiotics
15. Pregnancy, planned pregnancy within 3 months of study completion, or breastfeeding

Previous exclusion criteria:
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3. Previous or planned gastrointestinal IBD-related resectional surgery or previous cholecystectomy
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11.6. Severe liver disease;
11.7. Porphyria;
11.8. Congestive heart failure;
11.9. Coronary artery insufficiency;
11.10 Receiving concomitant drugs that prolong the QT interval (e.g. amiodarone, terfenadine, or sotalol)
12. Contraindications to the current use of ondansetron, including:
12.1. Concomitant use of apomorphine;
12.2. Concomitant use of other drugs that prolong the QT interval.
13. Contraindications to the current use of loperamide, including:
13.1. Acute UC;
13.2. Acute dysentery, which is characterised by blood in stools and high fever;
13.3. Bacterial enterocolitis caused by invasive organisms;
13.4. Pseudomembranous colitis associated with the use of broad-spectrum antibiotics
14. Pregnancy, planned pregnancy within 3 months of study completion, or breastfeeding

Date of first enrolment
01/04/2021

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon and Exeter NHS Hospital Foundation Trust
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Wolverhampton Hospitals NHS Trust
Wednesfield Road
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
St James's University Hospital (lead centre)
Leeds Teaching Hospitals Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 17/33/03

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.
CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor, and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.
The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.
The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree on suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		31/03/2025	09/05/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet version 1	11/11/2025	11/11/2025	No	Yes
Plain English results		09/02/2024	09/02/2024	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes