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A multi-centre, double-blind randomised controlled trial to compare Modafinil versus placebo over 12 weeks in patients with severe Fatigue and Inflammatory bowel disease (MFI): a feasibility study

Protocol Short Title/Acronym: Modafinil for fatigue in IBD (MFI)

MAIN SPONSOR: Imperial College London

FUNDER: Crohn's and Colitis UK and Jon Moulton Charity Trust

Clinicaltrials.gov number:

REC Number: 25/LO/0719

IRAS Project ID: 344329

Version: 1.0; 10/10/2025

Funding to conduct the trial is provided by Crohn's and Colitis UK and the Jon Moulton Charity Trust.

Clinical Queries

Clinical queries should be directed to Dr Calum Moulton (c.moulton@imperial.ac.uk) who will direct the query to the appropriate person.

Sponsor

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Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team

Imperial College London and Imperial College Healthcare NHS Trust

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Imperial College - Research Governance and Integrity Team (RGIT) Website

3. Study synopsis

Title of clinical trial	A multi-centre, double-blind randomised controlled trial to compare Modafinil versus placebo over 12 weeks in patients with severe Fatigue and inflammatory bowel disease (MFI): a feasibility study
Protocol Short Title/Acronym	MD-IBD
Study Phase, if not mentioned in title	Phase II Feasibility
Sponsor name	Imperial College London
Chief Investigator	Dr Calum Moulton
REC number	TBC
Medical condition or disease under investigation	Fatigue
Intervention of interest	Modafinil
Purpose of clinical trial	To test the feasibility of a definitive trial of modafinil versus placebo for the treatment of severe fatigue in patients with IBD.
Primary objective	To evaluate the feasibility of an RCT design by measuring recruitment rates, retention rates, adherence rates and patient acceptability, in order to inform the design of a phase 3 trial.
Secondary objective(s)	To assess the acceptability of the proposed data measures, as estimated using completeness of data. This will comprise

	questionnaire measures of mental health, quality of life and IBD control; measures of other gastrointestinal symptoms; blood measures of dopamine; and faecal sampling for calprotectin
Trial Design	Parallel group, double-blind, randomised, placebo-controlled, phase II feasibility design.
Endpoints	**Primary endpoints (feasibility)** 1) Recruitment rates 2) Attrition rates at 12 weeks post-randomisation 3) Treatment adherence: % of participants taking at least 75% of prescribed medication 4) Acceptability scores at 12-weeks post-randomisation 5) Study procedures acceptability and compliance: % of questionnaire data collected at primary endpoint (12 weeks) The questionnaire measures at 12 weeks are: I. IBD Fatigue Assessment Score (first 5 questions) II. FACIT Fatigue scale III. Chalder Fatigue Questionnaire IV. PHQ-9 depression V. GAD-7 anxiety VI. IBD control scale VII. Pittsburgh Sleep Quality Index VIII. Maudsley 3-item Visual Analogue Scale IX. Harvey Bradshaw Index for Crohn's disease patients (baseline and 12 weeks only) X. Simple Clinical Colitis Activity Index for patients with ulcerative colitis (baseline and 12 weeks only) XI. Dietary Screener Questionnaire (baseline and 12 weeks only) XII. EQ-5D-5L (quality of life) 2. Blood measures at 12 weeks: Serum dopamine 3. Faecal calprotectin measurement at 12 weeks **Secondary feasibility endpoints** Completeness and variance of the above questionnaire measures (except the HBI and SCCAI) at 6 weeks post-randomisation, as well as post-treatment at 18 weeks post-randomisation
Sample Size	N=70 (35 modafinil, 35 placebo)
Summary of Eligibility Criteria	**Inclusion criteria:** 1) Established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) according to clinical notes 2) Reported fatigue duration of 6 months or more

	3) Aged 18 years or over 4) Current IBD Fatigue Assessment Scale score ≥11/20 5) Use of contraception if female and of childbearing age. Female participants of childbearing age will require a negative serum/urine pregnancy test before starting the study and will also need to agree to use an acceptable form of contraception throughout the intervention period, e.g. long-acting reversible contraceptive. 6) Faecal calprotectin <250mcg/g within the last 3 months 7) Normal haemoglobin concentration (≥130g/L [men] and ≥120g/L [women]) within the last 3 months 8) Thyroid stimulating hormone (TSH) level 0.4-4.0 mU/L within last 3 months 9) Serum total B12 concentration (≥180 nanograms/L) within last 3 months 10) Able to provide written informed consent to enter the trial. **Exclusion criteria:** 1) Diagnosis of drug or alcohol dependence syndrome according to patient report or GP record. 2) Diagnosis of any dementia according to patient report or GP record. 3) Diagnosis of psychosis or schizophrenia according to patient report or GP record. 4) Diagnosis of bipolar disorder according to patient report or GP record. 5) Current active suicidal ideation on clinical assessment by study psychiatrist. 6) Current treatment with stimulant medication (e.g. methylphenidate), dopamine agonist (e.g. ropinirole), levo-dopa (L-DOPA), antipsychotic (e.g. olanzapine), avacopan, avaritinib, bosutinib, doravirine, grazoprevir, leniosilib, moboceritinib, Osimertinib, sofosbuvir, velpatasvir or voxilapravir 7) Contraindications to the administration of modafinil, as per the current SmPC. 8) Patient-reported hypersensitivity to modafinil 9) Non-registration with a GP or failure to consent to sharing of the GP summary care record and any psychiatric assessments held. 10) Currently enrolled in another drug trial or psychological therapy trial.

	11) Currently hospitalised for the treatment of IBD. 12) Currently being prescribed a course of budesonide or reducing course of prednisolone for IBD. 13) Planned change in IBD treatment within the next 12 weeks. 14) Currently breastfeeding, pregnant or planning pregnancy. 15) Diagnosis of indeterminate colitis
Medication, dosage and route of administration	Modafinil capsule total daily dose 100-300mg daily for 12 weeks (dose increased according to clinical response)
Comparator product(s)	Placebo capsules for 12 weeks (dose increased according to clinical response)
Maximum duration of treatment of a subject	12 weeks followed by 1-week tapering off dose
Follow up Duration	18 weeks post-randomisation (12 weeks of blinded treatment followed by 6 weeks of post-treatment follow-up)
Planned Trial Period	November 2025-November 2027
Funding	Jon Moulton Charity Trust Crohn's and Colitis UK
Version and Date of Final Protocol	Version 1.0, 10/10/25

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4. Abbreviations list

5-HT	5-hydroxytryptamine
AE	Adverse Event
BMI	Body mass index
CD	Crohn's disease
CFQ	Chalder Fatigue Questionnaire
CFS	Chronic fatigue syndrome
CONSORT	Consolidated Standards of Reporting Trials
CTA	Clinical Trials Authorisation
CTU	Clinical Trials Unit
DSM	Diagnostics and Statistical Manual
GAD-7	Generalised Anxiety Disorder-7
GP	General Practitioner
HBI	Harvey Bradshaw Index
HRA	Health Research Authority
IBD Control	Inflammatory Bowel Disease Control Questionnaire
IBD-Fatigue	Inflammatory Bowel Disease Fatigue Scale
M3VAS	Maudsley 3-item Visual Analogue Scale
ME	Myalgic encephalomyelitis
MedDRA	Medical Dictionary for Drug Regulatory Activities
MINI	MINI Neuropsychiatric Interview
NICE	National Institute for Health and Care Excellence
ON	Once at night
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders Symptom Severity Index
PSQI	Pittsburgh Sleep Quality Index
QIDS-SR-16	Quick Inventory of Depressive Symptomatology-16
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCCAI	Short Clinical Colitis Activity Index
SNRI	Serotonin and noradrenaline reuptake inhibitor
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitor
TAU	Treatment-as-usual
UC	Ulcerative colitis
USAR	Unexpected Serious Adverse Reaction

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Funder

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This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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5. Roles and responsibilities

5.1. Sponsor

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5.5. Committees

A trial management group will meet regularly to review trial progress. An independent trial steering committee (TSC) will meet between 6 months to 1 year during the duration of the trial.

5.5.1. Trial steering committee

We will follow NIHR Research Governance Guidelines (https://www.nihr.ac.uk/documents/research-governance-guidelines/) in setting up the Trial Steering Committee (TSC). As per NIHR guidance, the TSC will meet at least once per year and will be set up to monitor, review and supervise the progress of the trial. This will have an independent chair. We will invite 2-4 service user representatives onto the TSC. Alongside our statistical expertise, the Steering Committee review will ensure that conduct and reporting standards (e.g. stipulated by the Nature Publishing Group) are adhered to. This will include use of appropriate methodology and subsequent reporting (i.e. CONSORT checklist items, design, recruitment, allocation, blinding, ethics, trial registration), and statistical procedures (i.e. stating assumptions, comprehensive reporting of results and providing clearly labelled descriptive statistics and figures, along with a CONSORT flowchart). In accordance with NIHR guidelines, 67% of appointed members must attend TSC meetings to be deemed quorate.

The role of the TSC will be to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. We will carefully monitor adverse events and patient safety, and any concerns in this regard will be promptly taken to the CI and TSC. The main roles of the TSC are as follows:

- To provide advice, through its Chair, to the Chief Investigator, the Trial -sponsor, the Trial Funder and the Host Institution on all appropriate aspects of the trial
- To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the trial

In accordance with NIHR guidelines, at least 67% of the TSC will be independent. The independent members will sign the TSC terms of reference.

5.6. Role of sponsor and funder

The Funder was not involved in the design of the study and will not be involved in the management of the study. The sponsor helped to revise the protocol for clarity. The sponsor will provide overall oversight of the study. The Chief Investigator will take full responsibility for the decision to submit for publication.

6. Introduction

6.1. Background and rationale

Fatigue is highly prevalent in patients with IBD, affecting 72% of patients with active IBD and 47% in remission, and associated with poor quality of life and significant wider costs.[1] However, effective treatments are lacking.[2] Drug trials for IBD fatigue have been very few and unsuccesful.[2–4] As such, novel pharmacological treatments for IBD fatigue are needed. Modafinil is a central nervous system stimulant used since the 1980s to promote wakefulness in narcolepsy, producing a rapid benefit that wears off late in the day.[5] Modafinil primarily induces wakefulness by increasing available dopamine in the brain.[5] Modafinil can be used off-licence in patients with depression, producing improvement in depression and fatigue,[6] and such use is supported by clinical guidelines.[7] Modafinil also enhances cognitive performance.[8] Modafinil is safe with long-term use and has a low risk of adverse effects or dependence.[5] With no serotonergic and minimal noradrenergic effects, it is not expected to worsen any gut symptoms. To date, however, there are no trials of modafinil for fatigue in IBD.

Preliminary data: We recently published a case series of 10 patients with IBD and severe fatigue treated with modafinil. In this series, we found 58% improvement in fatigue and good tolerability.[9] Although the results presented were at 6-month follow-up, we found the same benefit only 2 months after starting treatment, which was sustained. Overall, in our clinical IBD fatigue service, we have used modafinil in 36 patients with IBD fatigue. Despite the cohort having very refractory IBD (56% already treated with multiple biologic therapies), modafinil produced a mean 41.4% improvement in fatigue severity after 3 months and was well tolerated.[10] Whereas all were in the severe fatigue range at baseline, only 36.1% remained so after modafinil treatment.

Summary: Our preliminary findings suggest that dopamine deficiency may be a key pathway to IBD fatigue. This complements growing genetic, epidemiological and mechanistic evidence of gut-brain dopamine deficiency in IBD.[7] However, measuring brain dopamine levels directly would require invasive and hugely expensive methods, such as positron emission technology (PET) imaging. Using modafinil – a dopamine reuptake inhibitor – provides a therapeutic test of this mechanism. Given that modafinil has never been trialled in patients with IBD, the necessary first step is a feasibility trial testing modafinil in patients with IBD.

7. Study objectives and design

7.1. Aim

To test whether it is feasible to carry out a trial of modafinil versus placebo – both in addition to treatment-as-usual – for the treatment of severe fatigue in patients with IBD, in order to inform the design of a subsequent powered multi-centre randomised controlled trial (RCT).

7.2. Objectives

The primary objective of the research is to test the feasibility of a definitive trial of modafinil + treatment-as-usual (TAU) against matched placebo + TAU for severe fatigue in adults with IBD. This study will:

1) Establish recruitment, retention, and adherence rates (see section 20.1 for feasibility outcomes with green/amber/red ranges)

2) Measure acceptability using treatment adherence (see section 20.1) and qualitative interview (see sections 13.9 and 20.3)

3) Test the assessment methods and procedures for measuring variables for use in a full trial, including the acceptability and completion rate of outcome measures (see section 12.4)

Secondary objectives

We will also estimate the completeness and variance (spread) in the following secondary outcomes:

1) Questionnaires:

I. General fatigue severity using the first 5 questions of the Inflammatory Bowel Disease-Fatigue questionnaire (https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/measure-your-fatigue)

II. The FACIT-F fatigue scale: a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function

III. Depression using the PHQ-9 questionnaire (1999 version), which has been validated in patients with IBD

IV. Anxiety using the GAD-7 questionnaire (1999 version), which has been validated in patients with IBD

V. IBD control measured using the IBD-Control questionnaire (2014 version)

VI. Mental and physical fatigue symptoms using the 11-item Chalder Fatigue Scale (1993 version)

VII. Sleep disturbance and quality using the Pittsburgh Sleep Quality Index (1989 version)

VIII. Core depressive symptoms using the Maudsley 3-item Visual Analogue Scale, which we previously validated (for participants being seen in person only)

IX. Harvey Bradshaw Index for Crohn's disease patients (baseline and week 12 only)21

X. Simple Clinical Colitis Activity Index for ulcerative colitis patients (baseline and week 12 only)

XI. Dietary Screener Questionnaire (baseline and week 12 only) from the NHANES 2009-10 study

XII. EQ-5D-5L (5-item quality of life questionnaire)

2) Blood levels of dopamine at baseline and 12 weeks

3) Faecal calprotectin level at baseline and 12 weeks

4) Hand grip strength at baseline and 12 weeks

8. Study design

The study is a parallel group, 1:1 feasibility randomised controlled trial (RCT). Participants will be randomised to one of the two treatment arms (modafinil + treatment-as-usual (TAU) or matched placebo + TAU) and will complete measures at baseline, 6 weeks and 12-weeks post randomisation. Blinded treatment will last for 12 weeks, followed by the offer of a 1-week tapering off dose. A post-treatment follow-up will take place at 18 weeks post-randomisation. This feasibility trial is designed to test "can this trial be done" and is not designed to assess clinical efficacy or safety of modafinil

against placebo. Assessment of safety is for participating adverse events and not to measure drug safety.

Methods: Participants, Interventions and Outcomes

9. Study setting

Patients will be recruited from outpatient gastroenterology services at King's College Hospital, St Mark's Hospital, Imperial College Healthcare NHS Foundation Trust, and Guy's and St Thomas' Hospital NHS Foundation Trust. For participants wishing to be reviewed in person, study visits will take place at the NIHR/Wellcome Clinical Research Facility at King's College Hospital, at St Mark's Hospital, Guy's and St Thomas' Hospital, and Imperial College Healthcare NHS Foundation Trust. Participants can also be reviewed online via MS Teams videolink if they prefer, with the exception of the baseline visit, which must be conducted in person.

10. Eligibility criteria

10.1. Inclusion criteria

Inclusion criteria:

1) Established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) according to clinical notes.

2) Reported fatigue duration of 6 months or more.

3) Aged 18 years or over.

4) Current IBD Fatigue Assessment Scale score ≥11/20.

5) Use of contraception if female and of childbearing age. Female participants of childbearing age will require a negative serum/urine pregnancy test before starting the study and will also need to agree to use an acceptable form of contraception throughout the intervention period, e.g. long-acting reversible contraceptive.

6) Faecal calprotectin <250mcg/g within the last 3 months.

7) Normal haemoglobin concentration (≥130g/L [men] and ≥120g/L [women]) within the last 3 months.

8) Thyroid stimulating hormone (TSH) level 0.4-4.0 mU/L within last 3 months.

9) Serum total B12 concentration (≥180 nanograms/L) within last 3 months.

10) Able to provide written informed consent to enter the trial.

10.2. Exclusion criteria

1) Diagnosis of drug or alcohol dependence syndrome according to patient report or GP record.

2) Diagnosis of any dementia according to patient report or GP record.

3) Diagnosis of psychosis or schizophrenia according to patient report or GP record.

4) Diagnosis of bipolar disorder according to patient report or GP record.

5) Current active suicidal ideation on clinical assessment by study psychiatrist.

6) Current treatment with stimulant medication (e.g. methylphenidate), dopamine agonist (e.g. ropinirole), antipsychotic (e.g. olanzapine), L-DOPA, avacopan, avaritinib, bosutinib, doravirine, grazoprevir, leniosilib, moboceritinib, Osimertinib, sofosbuvir, velpatasvir or voxilapravir

7) Contraindications to the administration of modafinil, as per the current SmPC.

8) Patient-reported hypersensitivity to modafinil

9) Non-registration with a GP or failure to consent to sharing of the GP summary care record and any psychiatric assessments held.

10) Currently enrolled in another drug trial or psychological therapy trial.

11) Currently hospitalised for the treatment of IBD.

12) Currently being prescribed a course of budesonide or reducing course of prednisolone for IBD.

13) Planned change in IBD treatment within the next 12 weeks.

14) Currently breastfeeding, pregnant or planning pregnancy

15) Diagnosis of indeterminate colitis

11. Intervention

11.1. Treatment arm

Half of the cohort (n=35) will be randomised to 12 weeks of treatment with modafinil, which will be blinded through over-encapsulation. The starting dose will be 100mg once in the morning. Treatment with modafinil will occur in addition to treatment-as-usual, which is antidepressant treatment or any psychological therapy the patient wishes to access through NHS services or private therapy services, although a typical wait for psychological therapy on the NHS is 3-6 months. The patient and assessor will remain blinded to treatment allocation throughout the 12 weeks of treatment. In order to avoid serious confounding of the findings in any confirmatory trial, patients will be asked not to change any IBD treatment or start any new antidepressants during the 12-week treatment period. If they do require a change in their IBD treatment, they will be withdrawn from the trial.

11.1.1. Modifications (treatment arm)

After 2 weeks, participants will be asked to increase to 100mg morning and 100mg lunchtime if they feel they need a higher dose and they are tolerating the treatment. After a further 2 weeks, participants will be asked to increase to the maximum dose of 200mg morning and 100mg lunchtime if they feel they need a higher dose and they are tolerating the treatment. Participants can increase their dose at longer intervals if they prefer, but will be asked not to increase to the maximum dose before 4 weeks.

11.2. Control arm

The other half of the cohort (n=35) will be randomised to a matched placebo, which is a matched capsule filled with lactose. Treatment with placebo will occur in addition to treatment-as-usual, which is antidepressant treatment or any psychological therapy the patient wishes to access through NHS services or private therapy services, although a typical wait for psychological therapy on the NHS is 3-6 months. The patient and assessor will remain blinded to treatment allocation throughout the 12 weeks of treatment. In order to avoid serious confounding of the findings in any confirmatory trial,

patients will be asked not to change any IBD treatment or start any new antidepressants during the 12-week treatment period. If they do require a change in their IBD treatment, they will be withdrawn from the trial. For procedures after the 12 weeks of treatment, see section 11.4.

11.2.2 Modifications (placebo arm)

After 2 weeks, participants will be asked to increase to 1 capsule in the morning and 1 capsule at lunchtime if they feel they need a higher dose and they are tolerating the treatment. After a further 2 weeks, participants will be asked to increase to the maximum dose of 2 capsules morning and 1 lunchtime if they feel they need a higher dose and they are tolerating the treatment. Participants can increase their dose at longer intervals if they prefer, but will be asked not to increase to the maximum dose before 4 weeks.

11.3. Adherence (both arms)

Adherence will be monitored through patient report and through pill counts. We will also capture reasons for non-adherence. Adherence reminders will take place at the initial product dispensing and each study visit thereafter. This session will include:

- The importance of following study guidelines for adherence to the dosing advice
- Instructions about taking study pills including dose timing, storage, and importance of taking pills whole, and what to do in the event of a missed dose (do not double-dose)
- Importance of calling the study team if experiencing problems possibly related to study product such as symptoms or lost pills

11.4. Continuity of care

Modafinil is not a licensed treatment for IBD fatigue and so routine continuation of care through primary care will not be offered to patients. All participants will be given a 1-week tapering supply with which to reduce their dose gradually and stop after the 12 weeks of treatment. Modafinil is not associated with discontinuation or withdrawal on cessation. Patients will be offered advice on alternative treatments they may be able to access for fatigue.

11.5. Concomitant medications

Modafinil can be combined with antidepressants or used without.[11] As such, prescription of these medications does not preclude participation in the study. However, patients taking stimulant medications will be excluded, owing to mechanistic overlap with modafinil. Likewise, patients will be excluded if they are taking antipsychotics, dopamine agonists or L-DOPA.

During the trial itself, changes in any depression medication or IBD medication could seriously confound the findings. Participants will therefore agree not to start any other antidepressants during the trial. In order to avoid serious confounding of the findings in any confirmatory trial, patients will be asked not to change any IBD treatment during the 12-week treatment period. To minimise the risk of this happening, we will exclude participants where there is a planned or expected change in IBD treatment in the next 12 weeks.

11.6. Medication risks

Summary of Product Characteristics (SmPC) for modafinil 100mg are the reference safety information (RSI) documents which detail the medication risks. Specifically, section 4.8 will be used to assess the relativeness of an adverse event with the medication.

11.7. Medication manufacture, packaging and labelling

Modafinil and placebo capsules will be manufactured by Newcastle Specials Pharmacy. Modafinil will be packaged into HDPE containers containing, respectively, 35 x 100mg modafinil. Participants will receive 7 of these containers to cover the maximum dose that could be required for the whole trial, in addition to a post-trial tapering supply. Placebo capsules will be packaged into identical containers containing 35 capsules and participants will be given 7 of these containers also. The placebo and modafinil capsules will be visually identical and in identical packaging Annex 13-compliant labels will be provided by Newcastle Specials Pharmacy. As pharmacy staff will not be blinded, the study product will be supplied to pharmacy in containers that will be clearly differentiated and then dispensed to researchers and participants in a blinded fashion. Tear-off labels will be used for pharmacy staff to identify the modafinil and the placebo. Medication will be sent to King's College Hospital by dedicated courier with temperature-controlled vehicles tracked from site to site.

11.8. Medication storage and dispensing

All study products will be stored at King's College Hospital Pharmacy according to manufacturer instructions (at room temperature). King's College Hospital Pharmacy will dispense the correct treatment arm to each participant against the unblinded kit number list provided by the KCTU. Refer to the Pharmacy Manual for further instructions. There will be one dispensing episodes: at baseline after baseline after baseline data collection and randomisation.

11.9. Treatment stopping rules

Treatment will be stopped for an individual participant if they develop any of the following:

- Active suicidal thoughts. Specifically, any participant who scores 2 or 3 on item 9 (suicidal thoughts) of the Patient Health Questionnaire-9 (PHQ-9) at any point in the trial or before, will undergo a clinical assessment of suicide risk by one of the trial psychiatrists. If such a participant is assessed as having active suicidal thoughts according to clinical assessment, they will be excluded from the trial or their treatment stopped
- Pregnancy
- Any Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR), which, in the view of the investigators, necessitates treatment cessation. For these events, the modafinil/placebo should be paused until resolution of the event. After this, the CI will make a clinical decision on the safety of re-introducing the modafinil/placebo

Treatment will also be stopped if requested by any participant at any time. The trial may be prematurely discontinued by the sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the regulatory authority or ethics committee concerned. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Research Ethics Committee will be informed within 15 days of the early termination of the trial.

Every effort will be made to ensure the patient outcomes are continued to be collected even if their treatment has been stopped.

11.9.1. Suicidality protocol

Anyone scoring 2/3 or 3/3 on item 9 on the PHQ-9 questionnaire ("Have you had thoughts that you would be better off dead, or of hurting yourself in some way?") will be asked the following question by the research team: "You mentioned you've been having thoughts that life is not worth living. Is that right?" If the patient replies yes or is unsure, they will be asked, "have you had any thoughts about taking your own life?" and "do you feel hopeless about the future?" If a patient replies yes to these questions or is not sure, one of the study team will contact the patient's GP and/or local crisis mental health services on the same day to report their concerns. A study psychiatrist will assess the patient and recommend trial treatment discontinuation if the patient is deemed actively suicidal. The research team will explain this to the patient. The study team will follow-up within 1 week to ensure that appropriate clinical follow-up has taken place.

In the very unlikely event that a patient is actively suicidal but refuses to let the research team contact their GP or local mental health services, a study psychiatrist will perform a more detailed assessment. They will explain their concerns to the patient and that most patients can be cared for in the community. If, however, the psychiatrist believes that the patient is at high risk of suicide yet they continue to refuse follow-up, the psychiatrist will advise that they will have to contact the police. If appropriate, the police can convey an actively suicidal patient to a place of safety under the Mental Health Act.

11.10. Withdrawal

Participants have the right to withdraw from the study at any time for any reason. The right to withdraw is clearly explained in the participant information sheet and consent form. The investigator also has the right to withdraw participants from the study in the event of inter-current illness, AEs, protocol or treatment non-compliance or administrative reasons. As an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw from the intervention, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

12. Outcomes

12.1. Feasibility and acceptability

1. Recruitment feasibility: participants randomised overall, % of target

2. Trial adherence: % of participants completing 12 weeks of treatment

3. Treatment adherence: % of participants taking at least 75% of prescribed mediation

4. Study procedures acceptability and compliance: % of planned data and samples collected at primary endpoint (12 weeks)

5. Overall acceptability: % participants describing the treatment as acceptable (≥6/10 on 0-10 scale)

12.2. Measures collected at baseline

The research team will collect the following data at the baseline visit:

Socio-demographic variables: data on age, sex, ethnicity (white, black, South Asian/other), occupational status, marital status (Married /Civil partnership, Living with a partner, Widowed, Divorced/Separated, Single, with a partner but not living together), current employment status (Employed full-time, Employed part-time, Full or part-time education, Full-time domestic responsibilities, Retired, Unemployed current/previous smoking status (number of cigarettes, cigars or vapes per day), and current alcohol use (none, 1-14 units per day, 15 or more units per day).

Psychiatric history: participants will be asked about previous episodes of depression or anxiety, medication history (including current and previous antidepressants), previous psychological therapies (Graded Exercise Therapy, Group-based Cognitive Behavioural Therapy, Individual Cognitive Behavioural Therapy, Counselling, [Short-term] psychodynamic therapy, Mindfulness Based Cognitive Therapy), and psychiatric comorbidities. Patients will also be asked about previous diagnoses of ME/CFS or long covid.

Other medical conditions: we will ask about conditions associated with fatigue, including liver disease, rheumatoid arthritis, coeliac disease. **Pain syndromes**: patients will be asked about previous diagnoses of fibromyalgia, migraine, chronic headache, chronic pelvic pain, temporomandibular joint dysfunction, endometriosis

Criteria for ME/CFS: patients will be assessed for NICE criteria for ME/CFS, which is diagnosed if all of the following are present for at least 6 weeks:

• Debilitating fatigue that is worsened by activity, is not caused by excessive cognitive, physical, emotional or social exertion, and is not significantly relieved by rest.

• Post-exertional malaise after activity in which the worsening of symptoms:

— is often delayed in onset by hours or days

— is disproportionate to the activity

— has a prolonged recovery time that may last hours, days, weeks or longer.

· Unrefreshing sleep or sleep disturbance (or both), which may include:

— feeling exhausted, feeling flu-like and stiff on waking

— broken or shallow sleep, altered sleep pattern or hypersomnia.

· Cognitive difficulties (sometimes described as 'brain fog'), which may include problems finding words or numbers, difficulty in speaking, slowed responsiveness, short-term memory problems, and difficulty concentrating or multitasking.

- The person's ability to engage in occupational, educational, social or personal activities is significantly reduced from pre-illness level

IBD variables: from the clinical notes, we will record IBD diagnosis, disease type using the Montreal classification, IBD duration, current medications, current analgesia, presence/absence of fistulae, current stoma, current parenteral nutrition or intravenous fluid support, and previous surgery (number of operations). Where these data are not available, we will ask patients. If not available within the last 3 months, participants will be asked to provide a faecal sample for calprotectin, which provides a measure of IBD disease activity.

Hand-grip strength (HGS) will be quantified using a Hand Dynamometer that measures isometric muscular strength of the hand and forearm. Participants will be seated with back, pelvis, and knees as close to 90 degrees as possible. The shoulder will be abducted and neutrally rotated with the elbow flexed at 90 degrees, the forearm neutral, and the wrist held between 0 and 15 degrees of ulnar deviation. The dynamometer will be presented vertically, in line with the forearm, to the participant's dominant hand. Participants will be instructed to squeeze the hand grip as hard as they can for 3 seconds, in three successive trials with 30 s in between each, with the best reading taken.

Bloods: where possible, if not completed in the last 3 months, a blood sample will be taken for CRP, serum micronutrient concentrations, including selenium, copper, zinc and a vitamin screen.

Hand-grip strength: Questionnaires: Participants will complete a questionnaire schedule that includes key psychological measures, typically completed within 30 minutes by patients themselves, and can therefore be completely remotely online if preferred (see section 12.4: 'secondary feasibility outcomes'). For this feasibility study, the primary aim is to assess the acceptability, spread and completeness of these questionnaire data.

Anthropometrics: Height and weight will be obtained.

12.3. Secondary feasibility outcomes (baseline, 6 weeks, 12 weeks and 18 weeks post-randomisation)

We will also estimate the completeness and variance in the following secondary outcomes:

1) Questionnaires (all reported as continuous scores):

I. General fatigue severity using the first 5 questions of the Inflammatory Bowel Disease-Fatigue questionnaire (https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/measure-your-fatigue)[12]
II. The FACIT-F fatigue scale: a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function
III. Depression using the PHQ-9 questionnaire (1999 version), which has been validated in patients with IBD[13,14]
IV. Anxiety using the GAD-7 questionnaire (1999 version), which has been validated in patients with IBD[14,15]
V. IBD control measured using the IBD-Control questionnaire (2014 version)[16]
VI. Mental and physical fatigue symptoms using the 11-item Chalder Fatigue Scale (1993 version)[17,18]
VII. Sleep disturbance and quality using the Pittsburgh Sleep Quality Index (1989 version)[19]
VIII. Core depressive symptoms using the Maudsley 3-item Visual Analogue Scale, which we previously validated[20] (for participants being seen in person only)
IX. Harvey Bradshaw Index for Crohn's disease patients (baseline and week 12 only)[21]
X. Simple Clinical Colitis Activity Index for ulcerative colitis patients (baseline and week 12 only)[22]
XI. Dietary Screener Questionnaire (baseline and week 12 only) from the NHANES 2009-10 study
XII. EQ-5D-5L (quality of life)

Assessments will be conducted either in person or remotely, according to patient preference.

2) Blood tests at baseline and 12 weeks post-randomisation (reported as continuous scores): We will draw blood and measure plasma dopamine.

3) Faecal calprotectin at baseline and 12 weeks post-randomisation (reported as continuous measurement and as proportion with cut-off ≥150µg/g; note that this is different from the 250µg/g; cut-off used for inclusion)

4**) Hand-grip strength (HGS)** will be repeated at 12 weeks, as per the baseline protocol.

12.4. Exploratory outcomes

A further sample will be extracted in a lithium tube to be used for global metabolomic analysis using full-length 16S rRNA gene sequencing. The results of this will be reported outside of this trial. Participant will also be asked to provide an additional faecal sample at baseline and at 12 weeks for analysis of faecal microbiome and metabolome. The results will also be reported outside of this trial. As well as being measured as outcomes, the following questionnaires (see section 12.4) will be collected as potential mediators of modafinil treatment response in a future powered trial: change in sleep quality (PSQI score), changes in plasma dopamine, and change in depression (PHQ-9 score).

13. Participant timeline

13.1. Summary of procedures by visit

Visit	**Pre-screening**	**Baseline**	**Week 6**	**Week 12**	**Week 18**
	Pre-Screening (Day -14 to Day 0)	**Consent & baseline measures (Day 0)**	**6 weeks (+/-7 days) after random-isation)**	**12 weeks (+/-7 days) after random-isation)**	**18 weeks (+/-7days) after random-isation)**
Administrative					
Informed consent**		X			
Randomisation		X			
Dispensing modafinil /placebo		X*			
Screening					
Demographics		X			
MINI depression interview		X			
IBD history	X	X			
Psychiatric history		X			
NICE diagnostic criteria for ME/CFS		X			
Eligibility assessment	X	X			
IBD Fatigue Scale (first 5 questions)	X	X			
Assessments					

0-10 acceptability score				X	
Chalder Fatigue Questionnaire		X	X	X	X
Dietary screener		X		X	
EQ-5D-5L		X	X	X	
FACIT-F scale		X	X	X	X
GAD-7		X	X	X	X
Hand Grip Strength		X		X	
Height (to calculate BMI)		X			
IBD Control		X	X	X	X
IBD-Fatigue Scale (first 5 questions)		X	X	X	X
M3VAS***		X	X	X	X
PHQ-9		X	X	X	X
PSQI		X	X	X	X
Short Clinical Colitis Activity Index (UC) or Harvey Bradshaw index (CD)		X		X	
Weight		X		X***	
Biological samples					
Faecal calprotectin***		X		X	
Serum cytokines and CRP***		X		X	
Blood for metabolomic analysis***		X		X	
Blood (plasma) dopamine		X		X	
Faecal sample for microbiome/ metabolomic analysis		X		X	
Monitoring					
Adverse events			X	X	X
Concomitant medication		X	X	X	X
Pill count				X	

*The first medication dispensing can happen on the same day as the baseline visit or within the following 4 days. If necessary, the medication can be sent via secure post; **Informed consent will be taken prior to the baseline measures being collected; ***Not for participants being reviewed remotely.

13.2. Pre-screening

If interested in taking part, patients will be asked a small set of basic pre-screening questions either in the clinic, over the phone or over videolink (IBD diagnosis, duration of fatigue, current medications, whether they are planned to change any IBD treatments in the next 12 weeks) to determine their suitability for the study before being asked to attend a screening visit. If they have not yet completed the IBD-Fatigue scale, they will be asked this over the phone to ensure their score is 11 or more. Before pre-screening, the research team will advise patients that the fatigue information they provide will be passed onto their clinical team - with their permission - even if they decide not to take part in the study. They will be advised that any other information about their IBD will not be retained by the study team if they do not wish to take part. If anyone has an elevated fatigue score but does not wish to take part in the study, the research team will seek the patient's permission to relay the fatigue score to their clinical team.

13.3. Setting of visits

For participants wishing to be reviewed in person, study visits will take place at King's College Hospital, Imperial College Healthcare NHS Foundation Trust, Guy's and St Thomas' Hospital or at St Mark's Hospital. Participants can also be reviewed online videolink (MS Teams or NHS attend anywhere) if they prefer, with the exception of the baseline visit, which will only be conducted in person.

13.4. Baseline visit

In person, full informed consent will be obtained and an assessment of eligibility will be performed according to the eligibility criteria outlined. The participant will complete the baseline study questionnaires. The MINI interview for depression will be performed and the NICE criteria for ME/CFS used (these two diagnostic assessments will not be repeated after the baseline visit). The participant will also be invited to provide a blood sample and have height and weight measured. If determined eligible, the participant will be randomized to modafinil or placebo.

At this visit or within the next 4 days, patients will be given their medication supply for the trial and given the dosing instructions. The patients will be given contact details for the investigator team. If patients are unable to receive the medication the same day, they will be sent medication via recorded post within 4 days of the baseline visit. Two weeks after starting the medication, the participant will receive a phonecall from the research team to reiterate the dosing instructions and to answer any questions that may have arisen.

13.5. Week 6 (+/- 7 days)

At these visits, we will collect the following measures, which can be done in person or online according to patient preference:

- All the baseline psychiatric questionnaires (except the HBI/SCCAI or dietary screener)
- All baseline questionnaires of IBD disease activity
- Concomitant medications for IBD or mental health (strong or weak opioids)
- Adverse events/reactions, coded according to the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 14.1)

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13.6. Week 12 visit (+/- 7 days)

We will collect the following measures:

- All the baseline psychiatric questionnaires
- All baseline questionnaires of IBD disease activity
- Concomitant medications for IBD or mental health
- Hand grip strength
- Averse events/reactions, coded according to the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 14.1).
- Weight (for participants attending in person)
- Repeat blood testing for plasma dopamine and metabolomic analysis
- Repeat faecal calprotectin and additional faecal sample for microbiome and metabolomic analysis
- Count of unused medication
- 0-10 overall acceptability scores of the trial

13.7. Week 18 (+/- 7 days)

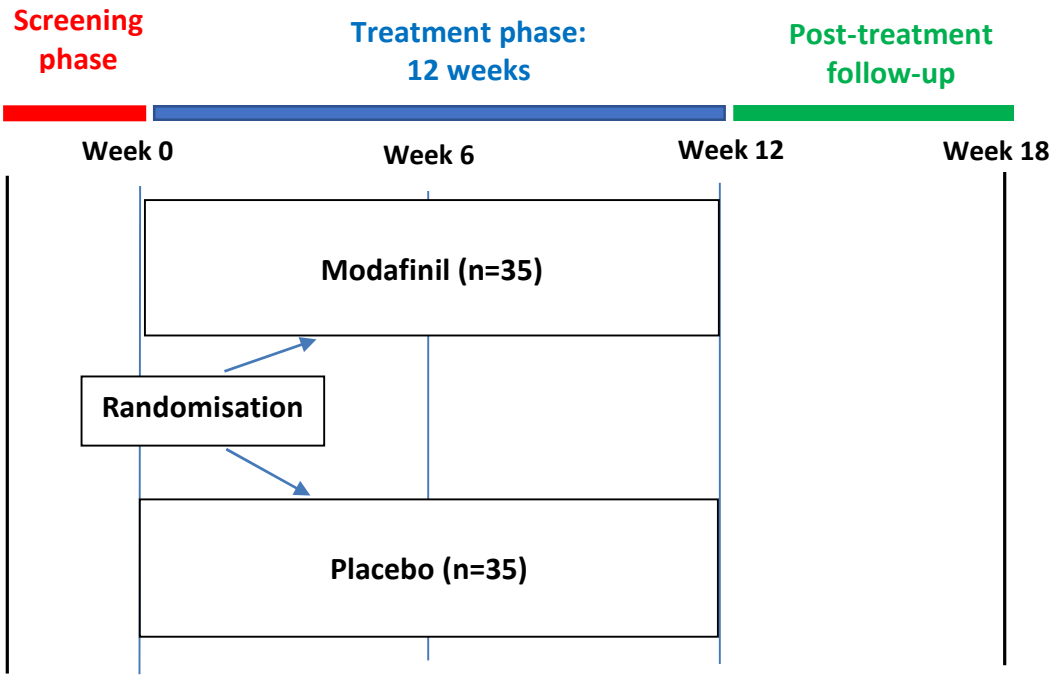
We will collect the following measures:

- All the baseline questionnaires (except the HBI/SCCAI and Dietary Screener)
- Concomitant medications for IBD or mental health
- Averse events/reactions, coded according to the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 14.1).

13.8. End of study definition

The end of the trial will be defined as the date when all participants have made their final visits.

13.9. Flow diagram



14. Sample size

As a feasibility study, power calculations for a treatment effect are not applicable. The target sample size is 70 participants (35 per group), which is sufficient to generate robust variance estimates.[23] To account for an estimated 15% attrition, we will recruit 70 participants to the study. Based on this sample size, a two-sided confidence interval will extend no more than 12% of the observed proportion.[24]

15. Recruitment

Consecutive patients aged ≥18 and diagnosed with IBD, confirmed using clinical notes, with self-reported fatigue will be identified. Where possible, they will be screened for severe fatigue using the first 5 questions of the IBD Fatigue Scale (the fatigue assessment component) as part of outpatient clinical care. For those with suspected severe fatigue, the clinical team will seek the patient's permission to be contacted by the research team. If they agree, the research team will then contact the patient – either in the clinic or over the phone – and provide the patient information sheet. Those who are deemed to be potentially eligible will be invited for a screening assessment with a member of the study team. Final study inclusion and consent will be taken by a member of the study team.

Recruitment will be maximised, where possible, by active psychological screening within clinical care at some of the participating centres. If necessary, further patients will be identified from screening of endoscopy schedules and IBD multidisciplinary team meetings. In addition, regular meetings will be held between the CI and research assistant/associate to scrutinise recruitment rates and enact contingency plans if necessary, including 1. Wider advertising about the study; 2. Widening recruitment to other sites; 3. Increased support from the Clinical Research Network; and 4. Recruitment through the My IBD Care app, which uses the PHQ-9 and for which several hundred patients at King's College Hospital are registered.

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Methods: Assignment of interventions

16. Allocation

Participants will be randomised into the study after providing informed consent and meeting the study selection criteria. Each participant will be assigned a unique identification number and randomised at the individual level prior to starting treatment.

16.1. Sequence generation

Participants will be randomly assigned to either modafinil or placebo with a 1:1 allocation as per a computer-generated randomisation schedule, which will use a varying permuted block design stratified by diagnosis (CD/UC) and sex assigned at birth (male/female). The block sizes will not be disclosed to ensure concealment. Participants will be randomised by the clinical team using a web based online the KCL Clinical Trials Unit (KCTU) randomisation system.

16.2. Concealment mechanism

Allocation concealment will be ensured, as the KCU randomisation service will not release the randomisation code which takes place after all baseline measurements have been completed.

16.3. Implementation

All patients who give consent for participation and who fulfil the inclusion criteria will be randomised before starting any treatment. Randomisation will be requested by the research team. The central randomisation service will send a form to the dispensing pharmacy that includes a randomisation number. In the pharmacy, closed envelopes with printed randomisation numbers will be available. For every randomisation number, the corresponding code for the treatment group of the randomisation list will be found inside the envelopes. The pharmacist will open the envelope and will find the treatment (modafinil or placebo) to be allocated to this patient. They will then dispense the medication to the patient. The study team and patient will not receive information about the group allocation. Throughout the study, the randomisation will be conducted by the KCTU in order to keep the data management and the statistician blind against the study condition as long as the data bank is open. The randomisation list remains with the KCTU for the whole duration of the study. Thus, randomisation will be conducted without any influence of the study team. Unblinding will occur after completion of all data analysis, on approval by the Chief Investigator.

17. Blinding

Participants and researchers will be blind to treatment allocation. The blinding will be maintained by opaque over-encapsulation of the modafinil/placebo. Assessments regarding clinical outcomes will be conducted by an assessor blind to treatment allocation. The trial statistician will become unblind after the first version of the Statistical Analysis Plan is signed. KCH pharmacy will provide blinded labelling and kit number allocation.

This is a low-risk intervention and we do not foresee any circumstances under which emergency unblinding would be required. Nevertheless, if the patient's clinician or study team believe that emergency unblinding is required, the Chief Investigator will contact the KCH trials pharmacy team and ask them to reveal the patient's treatment allocation. Such a participant would be removed from the trial.

18. Data collection methods

Subjects will be initially screened for possible severe fatigue using the IBD Fatigue questionnaire, using a cut-off score of 11 or more. This cut-off is validated in patients with IBD. Participants will be assessed for diagnostic criteria for ME/CFS using the NICE Guideline criteria, though inclusion is based on the IBD-Fatigue scale and not the NICE criteria. Participants will also undergo diagnostic interview for major depression using the MINI Neuropsychiatric Interview. This is a structured clinical interview that diagnoses MDD according to diagnostic criteria. It performs comparably with much longer semi-structured interviews,[25] yet can be completed in around 5-10 minutes, thereby minimising participant burden. The remaining questionnaires are self-report.

Anyone collecting data will be trained centrally in the study requirements, standardized measurement of height and weight, requirements for laboratory specimen collection, and the eliciting of information from study participants in a uniform reproducible manner.

Every effort will be made to ensure the patient outcomes are continued to be collected even if their treatment has been stopped.

19. Data management

Data will be collected on paper case report form (CRF) – this will be the source data - and then transferred to the MACRO electronic case report form (eCRF). Referential data rules, valid values, range checks, and consistency checks against data already stored in the database (i.e., longitudinal checks) are supported by the MACRO eCRF. The study team will resolve any queries identified by the eCRF checking function, cross-referencing with the source data. Where the original value is ambiguous, the data will be marked as absent. Data entered into the database will be retrievable for viewing through the data entry applications. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password. All forms and tapes related to study data will be kept in locked cabinets. Access to the study data will be restricted. The database will be password-protected.

20. Statistical methods

A statistical analysis plan (SAP) will be drafted using KCTU SOPs prior to database lock (ST:02, SAP) and approved by a blinded senior statistician and the TSC independent statistician. The results will be reported following CONSORT guidelines. The analysis population will use intention-to-treat principles. A recruitment plot of predicted vs. actual recruitment will be generated on a monthly basis.

20.1. Feasibility outcomes analyses

The milestones for progression to a full efficacy clinical trial will be as follows:

Outcome	Green (go)	Amber (amend)	Red (no-go)

	N=70	N=70	N=70
Recruitment feasibility: participants randomised overall, % of target	**80%** (≥56)	**60-79% (42-55)**	**<60% (<42)**
Trial adherence: % of participants completing 12 weeks of treatment	**75%** (≥53)	**60-74% (42-52)**	**<60% (<42)**
Treatment adherence: % of participants taking at least 75% of prescribed mediation	**75%** (≥53)	**50-74% (35-52)**	**<50% (<35)**
Study procedures acceptability and compliance: % of questionnaire data collected at primary endpoint	**80%** (≥56)	**60-79% (42-55)**	**<60% (<42)**
Overall acceptability for both arms: % participants describing the treatment as acceptable (≥6/10 on 0-10 scale)	**70%** (≥49)	**50-69% (35-48)**	**<50% (<35)**

20.2. Quantitative data analysis

Quantitative data analysis will be primarily descriptive to aid the planning of a future RCT. Participant flow through the study will be presented following CONSORT guidelines. Descriptive data will be presented in the form of means and standard deviations; medians and ranges; or percentages with 95% confidence intervals, as appropriate depending on the data being described.

We will use linear mixed models to estimate the between group adjusted mean difference (aMD) between modafinil and placebo groups at week 12 after adjustment for baseline scores, time, and a treatment-by-time-interaction. Associated 95% confidence intervals will be presented alongside the aMD without p-values.[26] More details will be provided in the SAP.

As the study is not powered to find treatment differences, the analysis will be preliminary and only used to inform the design of a full trial.

20.4. Exploratory analysis

To explore potential mediators of treatment response in a future powered trial (reduction in plasma dopamine, improvement in sleep quality [PSQI score], improvement in depression), exploratory analysis will report the mediation analysis. A directed acyclic graph (DAG) will be proposed to support

the causal inference. Significant findings will be interpreted cautiously, acknowledging the issue of multiple testing, need for replication and low statistical power.

Methods: Monitoring

21. Data monitoring

As this is a feasibility study using a low-risk intervention, no data monitoring committee will be formed for this trial. No interim analyses will be performed.

Harms

22. Assessment of safety

Data on Adverse Events will be collected with open ended questions and recorded systematically. Any reported events will be reviewed by the Investigator. The standard definitions of Adverse events/ Serious Adverse Events for medicinal products will be used, as follows:

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Medical judgement will be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, will also be considered serious.

22.1. Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort

Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.

Expectedness

Category	Definition
Expected	An adverse event which is consistent with the available information about the intervention/treatment/procedure in use in this study.
Unexpected	An adverse event which is not consistent with the available information about the intervention/treatment/procedure in use in this study*

* this includes listed events that are more frequently reported or more severe than previously reported

22.2. Procedures for recording adverse events

All such events, whether expected or not, should be recorded.

All Adverse events will be recorded in the CRF and in the medical notes following consent.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

22.3. Procedures for recording and reporting Serious Adverse Events

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the REC where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor (RGIT@imperial.ac.uk) and/or Research & Development Office.

All serious adverse events will be recorded in the medical records and the CRF.

All SAEs must be recorded on a serious adverse event (SAE) form. The PI or designated individual will complete an SAE form and the form will be preferably emailed to the Chief Investigator (c.moulton@imperial.ac.uk) within 1 working day of becoming aware of the event. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.within 5 working days.

22.4. Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC, Health Research Authority and R&I office of the measures taken and the circumstances giving rise to those measures.

22.5. Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI (with guidance from the trial statistician) and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

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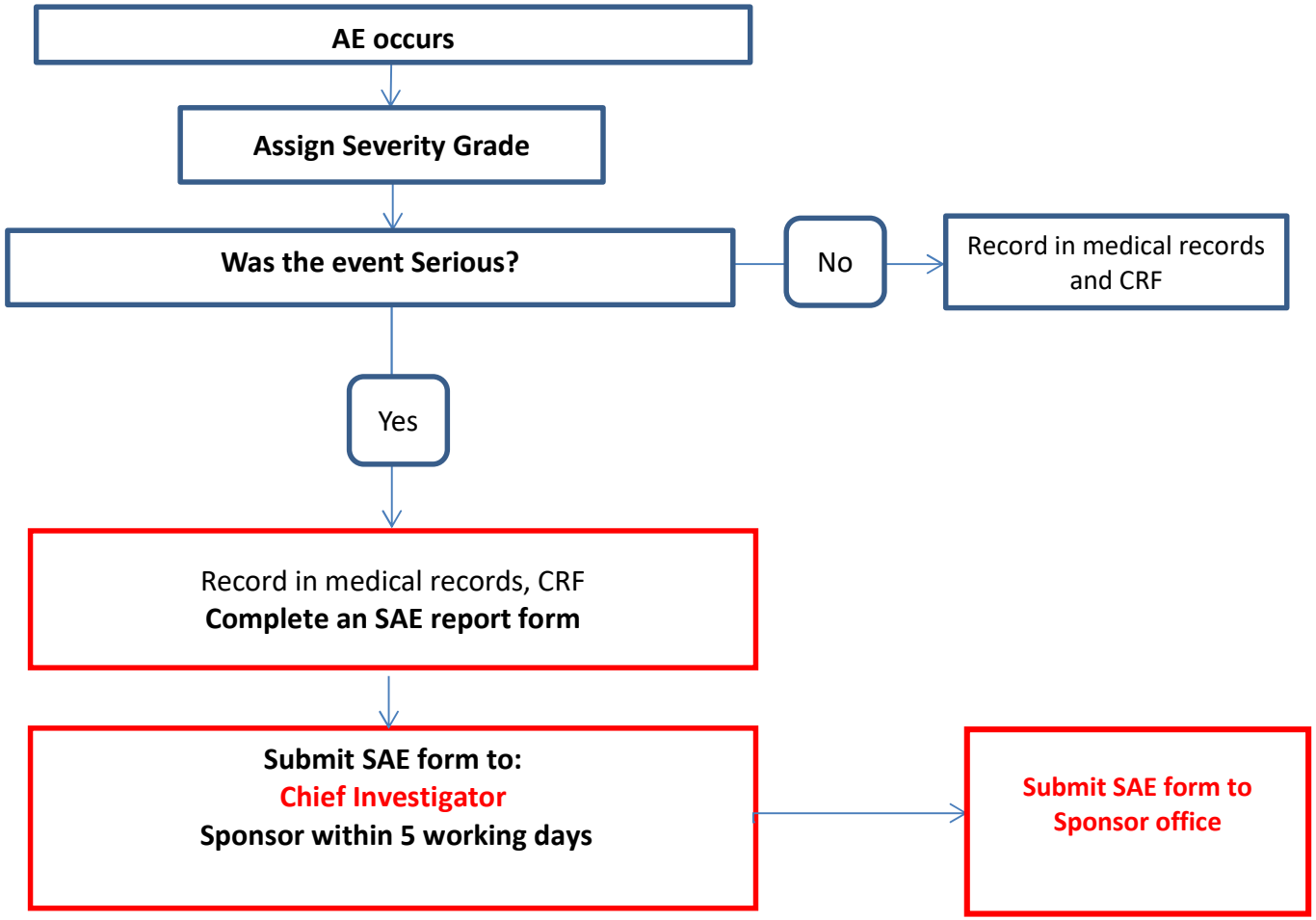
Flow Chart for SAE reporting



22.6. Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

22.7. Incidental findings

In this study, a likely incidental finding is of depression or suicidal ideation. This will be identified using the MINI interview and PHQ-9 questionnaire. These findings will be communicated by the study team to the patient's GP (see section 11.9.1 for suicidality protocol). The other likely incidental finding is of a raised faecal calprotectin or CRP concentration. These will be communicated to the patient's gastroenterology clinical team.

23. Auditing

According to the UK Policy Framework for Health and Social Care Research (section 9.2), part of the Chief Investigators responsibilities involves "adhering to the agreed procedures and arrangements for reporting (e.g. progress reports, safety reports) and for monitoring the research, including its conduct, the participants' safety and well-being and the ongoing suitability of the approved proposal or protocol in light of adverse events or other developments". The Chief Investigator will therefore ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include at least annual monitoring visits at each site. Monitoring will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

As sponsor, Imperial R&D carry out audits of studies and check how studies are performing during quarterly portfolio review meetings.

Ethics and Dissemination

24. Research ethics approval

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice in research (GCP), the CONSORT statement and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. The Chief Investigator will ensure that REC Favourable Opinion, HRA approval is in place before recruitment for the study begins. They will also ensure that

Confirmation of Capacity and Capability is in place at the relevant recruitment sites before recruitment at that site study begins. This protocol and other study documents have been submitted for review to the Queen's Square Research Ethics Committee.

25. Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the Trial Management Group and sponsor and approved by the Ethics Committee/HRA.

26. Consent

The Principal Investigator, or appropriately trained psychiatrist or gastroenterologist delegated by the Principal Investigator as documented in the site delegation log, will obtain written informed consent from each participant prior to any study specific procedures. Informed consent will be taken in person. The Informed Consent procedure will be preceded by an adequate explanation of the aims, methods, anticipated benefits and potential risks of the study. The participant will be given ample time to consider giving their consent for the study. It will be explained to the potential participant that they are free to refuse participation or alternatively withdraw their consent at any point during the study and for any reason. All participants who are actively enrolled on the study will be informed of any updated safety information which may result in significant changes in the risk/benefit analysis and will be re-consented to confirm their wish to continue the study.

27. Confidentiality

The Chief Investigator will act as custodian for the study data. All participant data written on paper will be anonymised and stored in password-protected files. Paper forms of participant data will be stored securely on site in locked filing cabinets. Information with regards to study subjects will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. Data will be stored for 5 years after study completion and will be archived according to Imperial College London policy. During study visits, data will be collected on paper Case Report Forms (CRFs) and then transferred to a secure web-based electronic database (MACRO). All electronic data entries will be regularly verified with source data.

28. Declaration of interests

The Chief Investigator and co-investigators have no conflicts of interests to declare that are relevant to this trial.

29. Access to data

The Chief Investigator will act as custodian for the study data. Access to anonymised data will be granted to other researchers upon reasonable request.

30. Ancillary and post-trial care

Although stopping modafinil is not associated with any withdrawal, we will provide patients with an extra 1-week supply that enables them to stop their dose gradually at the end of the trial. As modafinil is not a licensed treatment for fatigue, we are not routinely able to offer ongoing treatment after the trial. We will advise patients of any other treatments that may help their fatigue, such as antidepressants, and liaise with their GP as appropriate.

31. Dissemination policy

Findings of this feasibility study will be disseminated through international conferences, peer-reviewed journals, charities and educational seminars in acute trusts. If the study is feasible, it will support an application for a powered trial of modafinil for depression in IBD, for example through the NIHR Efficacy and Mechanism Evaluation Scheme. An expert IBD patient panel will advise on this Fellowship and on the dissemination of the study findings and developing future grant applications.

32. Sample handling

Blood samples will be collected at baseline and week 12. Blood samples will be collected by a phlebotomy-trained nurse or member of the research team and labelled with a unique barcode that includes the participant number and study identifier. The samples will then be taken directly to the Affinity Biolabs Laboratory. Those taken from other hospitals will be transported by validated courier. The analyses will be performed by the Affinity Biolabs laboratory and the results returned to the study team via email. Samples will be stored and processed in accordance with strict health and safety guidelines and under the requirements of the Human Tissue Act. The samples will only be used for the purposes of this study and then discarded.

Prior to the baseline visit, participants will be given a faecal sample pot and asked to provide a faecal sample for calprotectin (a measure of IBD disease activity). They will bring this sample with them on the day of the baseline visit. The sample will be analysed by Affinity Biolabs using an enzyme immunoassay. Participants will be provided with a second sample pot and asked to repeat the sample on the day of 12-week visit. This will also be analysed by Affinity Biolabs.

Participants may also be asked to provide an additional blood sample (taken in a lithium heparin tube) for metabolomic analysis, as well as a faecal sample for future microbiome and metabolomic analysis in the laboratory of Professor Julian Marchesi and Professor Nick Powell, Imperial College London.

33. Timeframe

This 24-month study includes up to 5 months for setup and approval, 12 months for recruitment (plus 3 months' contingency), 4 months for follow-up visits (including post-treatment follow-ups and qualitative interviews) and 3 months for write-up and dissemination.

34. Study participant support and reimbursement

Participants can contact the study team on a dedicated phone for 24 hours per day, for example to report adverse effects. Participants can choose to have questionnaire/interview assessments in person or virtually. Participants will receive a voucher of £40 each to compensate for inconvenience, as well as reimbursement of reasonable travel expenses. Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

35. Insurance/indemnity

Imperial College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that Imperial College has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. Imperial College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

36. Signatures

_____ _____ ____13/10/2025_____

Chief Investigator Date

Print Name: Dr Calum Moulton

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37. References

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