UCL Comprehensive Clinical Trials Unit

Short title:

MOTILITY (**M**RI **O**r **T**raditional **I**ndices for ear**L**y response prediction **I**n Biological **T**herap**Y**)

Full title:

MOTILITY: Small bowel motility quantified by cine MRI as a predictor of long term response in patients with Crohn's disease commencing biological therapy

Version	6.0
Date	28/04/2022
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2014/159
Trial registration	ISRCTN14481560
NRES #	17/WM/0106

Authorisation: Co Chief Investigator

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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 4. It describes the MOTILITY study, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the study, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, study population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the study; replication of key aspects of study methods and conduct; and appraisal of the study's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the study. Sites entering participants for the first time should confirm they have the correct version through a member of the study team at CCTU.

CCTU supports the commitment that its studies adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials[1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the study, or
- The scientific value of the study.

1.2 Sponsor

UCL is the study sponsor and has delegated responsibility for the overall management of the MOTILITY study to CCTU. Queries relating to UCL sponsorship of this study should be addressed to the CCTU Director or via the study team.

1.3 Structured study summary

Primary Registry and Study Identifying Number	ISRCTN14481560	
Date of Registration in Primary Registry	20th April 2017	
Secondary Identifying Numbers	CTU/2014/159	
Source of Monetary or Material Support	National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme (EME 14/201/16)	
Sponsor	University College London with sponsor responsibilities delegated to CCTU.	
Contact for Public Queries	ctu.enquiries@ucl.ac.uk	
Contact for Scientific Queries	Stuart Taylor Professor of Medical Imaging Centre for Medical Imaging Podium Level 2 235 Euston Rd London NW1 2BU stuart.taylor1@nhs.net 020 3549 5659 (PA)	Dr Andrew Plumb Associate Professor of Medical Imaging Centre for Medical Imaging Podium Level 2 235 Euston Rd London NW1 2BU andrew.plumb@nhs.net 020 3549 5659 (PA)
Public Title	MOTILITY (**M**RI **O**r **T**raditional **I**ndices for ear**L**y response prediction **I**n biological **T**herap**Y**)	
Scientific Title	MOTILITY: Small bowel motility quantified by cine MRI as a predictor of long term response in patients with Crohn's disease commencing biological therapy	
Countries of Recruitment	England	
Health Condition(s) or Problem(s) Studied	Crohn's disease patients scheduled to commence anti-TNFα or anti-interleukin therapy as part of their routine clinical care	
Intervention(s)	• Magnetic Resonance Imaging (MRI), a medical imaging technique using powerful magnetic fields and radiofrequency waves to generate detailed images of internal body structures. Patients drink liquid to distend the bowel and stimulate movement; rapid MRI images allow "cine" imaging of this bowel motion, which can be measured and quantified using software. • C-reactive protein (CRP) measurements, a blood test that measures plasma concentration of a protein produced by the body in response to inflammation. • Faecal calprotectin (fC) measurements, a stool test that measures the level of a granulocyte protein that is released into the bowel in response to inflammation. There is no control arm for this cohort study, and no change to normal clinical treatment. Patients will undergo tests at baseline (prior to starting / changing eligible biological treatment), after 12-30 weeks of treatment, and at the end of the study depending on clinical requirements. We will	

	compare the ability of each of the three tests to predict which patients respond to biological therapy.
Key Inclusion and Exclusion Criteria	**Inclusion criteria**: • Patients aged 16yrs or more with active luminal small bowel Crohn's disease, with or without colonic disease • Disease distribution and activity documented by ileocolonoscopy or (for patients with endoscopically-inaccessible disease) magnetic resonance enterography (MRE), enteric ultrasound (US), computed tomography (CT), barium fluoroscopic follow – through (BaFT) or video capsule endoscopy (VCE) performed as part of usual clinical care within the previous 90 days prior to starting eligible biological therapy or within 14 days after first treatment dose • Commenced or scheduled to commence or recommence eligible biological treatment (including biosimilars); specifically anti-TNF and anti-interleukin agents. If commenced treatment, consent should be obtained within 14 days after first treatment dose if motility sequences are not done as part of Standard of Care scan. • The primary target of therapy, in the opinion of the treating physician, is small bowel disease (with or without treatment of concomitant colonic disease). **Exclusion criteria**: • Biological therapies other than anti-TNF and anti-interleukin agents, such as anti – integrin therapy (e.g. Vedolizumab) • Primary target of therapy is limited to colonic or perianal fistulising disease • mMRI contraindicated (e.g. MRI-incompatible cardiac pacemaker, unable to lie flat, pregnancy) • Any psychiatric or other disorder precluding informed consent • Small bowel surgery within the preceding 90 days • Small bowel stricture causing upstream dilatation on imaging or endoscopy (defined as a >50% increase in diameter in comparison to the adjacent small bowel segment)
Study Type	Non-randomised, prospective, multicentre cohort study. Image interpretation and quantitation will be conducted by radiologists who are blinded to clinical data
Date of First Enrolment	May 2017
Target Sample Size	240
Primary Outcome(s)	Difference in sensitivity between stable or improved MRI-measured segmental small bowel motility versus normalisation of CRP at 12-30 weeks to predict response or remission (RoR) to anti-TNFα or anti-interleukin therapy at 1 year.
Key Secondary Outcomes	1. Difference in specificity between stable or improved MRI-measured small bowel motility *versus* normalisation of C-reactive protein at week 12-30 to predict RoR. 2. Difference in area under the receiver operating characteristic curve (ROC AUC) between changes from baseline to the week 12-30 in continuous small bowel motility MR score and in C-reactive protein levels to predict RoR. 3. Difference in prognostic accuracy between changes in the continuous small bowel motility MR score *versus* changes in C-reactive protein levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure (EQ-5D-5L, CUCQ-8 and IBD-Control 8).

	4. Difference in (i) sensitivity and (ii) specificity between stable or improved MRI-measured small bowel motility and normalisation of faecal calprotectin at week 12-30 for predicting RoR. Difference in (iii) ROC AUC between changes from baseline to week 12-30 in small bowel motility and in faecal calprotectin for predicting RoR. 5. Difference in prognostic accuracy between changes in the continuous MRI-measured small bowel motility score *versus* changes in faecal calprotectin levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure. 6. Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including MRI-measured small bowel motility *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to anti-TNFα or anti-interleukin therapy at one year. 7. Interobserver variability of MRI-measured small bowel motility for (a) experts in mMRI and (b) experienced radiologists without prior mMRI experience. Intraobserver variability of MRI-measured small bowel motility for experts in mMRI. 8. Difference in (a) plasma levels of (i) gut peptides and (ii) inflammatory cytokines and (b) small bowel motility variance between patients with and without RoR. 9. Difference in small bowel motility variance between patients with normal and elevated levels of (a) gut peptides (b) inflammatory cytokines and (c) between patients with and without abdominal symptoms at each time point. 10. Difference in response rates to anti-TNFα or anti-interleukin therapy at one year for (a) patients with and without skeletal muscle myopenia and (b) patients with and without low skeletal muscle:fat ratios. 11. Sensitivity and specificity of (a) >10% increase in ADC and (b) >25% reduction in Clermont score between weeks 0 and 12-30 for RoR to biologic therapy at one year. 12. Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including change in ADC value derived from DW-MRI between baseline and week 12-30 *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year. 13. Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including the Clermont score derived from DW-MRI *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year. 14. Difference in prognostic accuracy between changes in the Clermont score *versus* changes in (i) C-reactive protein and (ii) faecal calprotectin levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure. 15. Incremental prognostic value of DW-MRI parameters in conjunction with motility MRI scores for response to biologic therapy at one year. 16.

1.4 Roles and responsibilities

These membership lists are correct at the time of writing and will be updated with subsequent protocol amendments; please see terms of reference documentation in the Trial Master File for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Professor Stuart Taylor	UCL Medicine	Co-Chief Investigator
Dr Andrew Plumb	UCL Medicine	Co-Chief Investigator
Professor Caroline Doré	UCL CCTU	Statistical oversight
Kate Bennett	UCL CCTU	Study statistician
Zainib Shabir	UCL CCTU	Clinical project manager
Dr Marta Campos	UCL CCTU	Clinical project manager
Anvi Wadke	UCL CCTU	Study manager
Grace Auld	UCL CCTU	Clinical Project manager
Norin Ahmed	UCL CCTU	Study statistician
Kashfia Chowdhury	UCL CCTU	Statistical Oversight

1.4.2 Role of study sponsor and funders

Name	Affiliation	Role
UCL	UCL	Sponsor
CCTU	UCL	Delegated role as sponsor; study management, governance, data management, recruitment of study staff. UCL CCTU staff will lead data analysis and assist with interpretation of data and writing of the study report. Relevant CCTU staff will be involved in the decision to submit for publication, with the TMG and writing committee.
Efficacy and Mechanism Evaluation Programme	NIHR and MRC partnership	Funder; no influence over data collection, interpretation or decision to submit for publication

1.4.3 Study Team

Name	Affiliation	Role and responsibilities
Grace Auld	UCL CCTU	Clinical project manager
Sue Philpott	UCL CCTU	Study manager
Norin Ahmed	UCL CCTU	Study statistician
Victoria Danque	UCL CCTU	Data manager

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Stuart Taylor	UCL Medicine	Co-Chief Investigator & Radiologist
Dr Andrew Plumb	UCL Medicine	Co-Chief Investigator & Radiologist
Professor Simon Travis	Oxford	Gastroenterologist
Dr Damian Tolan	Leeds	Radiologist
Dr Arun Gupta	St Mark's	Radiologist
Dr Andy Slater	Oxford	Radiologist
Professor Steve Halligan	UCL Medicine	Radiologist
Ilan Jacobs	Citigroup	Patient representative
Kashfia Chowdhury	UCL CCTU	Statistical oversight
Norin Ahmed	UCL CCTU	Study Statistician
Grace Auld	UCL CCTU	Clinical project manager
Sue Philpott	UCL CCTU	Study manager
Principal Investigators from all recruiting sites (a complete list will be made available on request).		

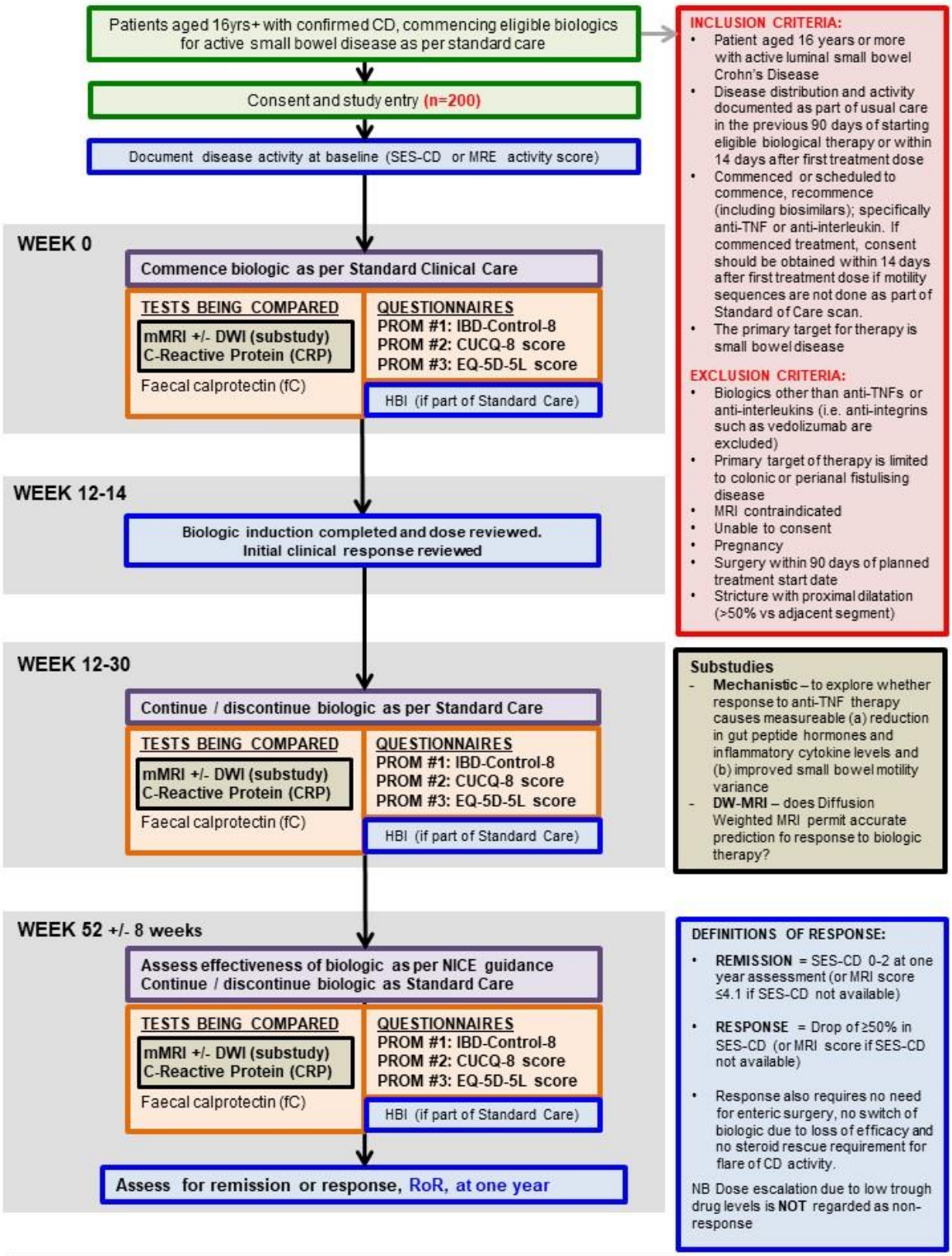
1.4.5 Joint Data Monitoring and Trial Steering Committee

Name	Affiliation	Role and responsibilities
Jeremy Sanderson	Kings College London	Consultant Gastroenterologist
Barney Hawthorne	University Hospital of Wales	Consultant Gastroenterologist
Ian Zealley	Ninewells Hospital	Consultant & Honorary Senior Clinical Lecturer
Graeme MacLennan	University of Aberdeen	Senior Statistician

1.4.6 Independent Safety Clinician

Name	Affiliation	Role and responsibilities
David Sanders	Sheffield	Consultant Gastroenterologist

Study Diagram



HBI=Harvey Bradshaw Index; CUCQ-8 = Crohn's and Ulcerative Colitis Questionnaire-8 item; EQ-5D-5L = European Quality of Life 5 dimension, 5 level; mMRI=motility MRI; DWI = diffusion-weighted imaging; ROC AUC=area under the receiver operating characteristic curve

Abbreviations

ADA	Adalimumab
AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
BSG	British Society of Gastroenterology
BSGAR	British Society of Gastrointestinal and Abdominal Radiology
CUCQ-8	Crohn's and Ulcerative Colitis Questionnaire, 8 item
CD	Crohn's Disease
CI	Chief Investigator
CRF	Case Report Form
CRP	C-Reactive Protein
CCTU	Comprehensive Clinical Trials Unit
DSUR	Development Safety Update Report
EQ5D5L	European Quality of life score, 5 Dimension, 5 Level
EU	European Union
FC	Faecal Calprotectin
FDA	(US) Food and Drug Administration
FRCR	Fellow of the Royal College of Radiologists
GCP	Good Clinical Practice
GLP-1	Glucagon-Like Peptide 1
HBI	Harvey Bradshaw Index
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFX	Infliximab
IL	Interleukin
IRB	Institutional Review Board
ITT	Intention to Treat
mAbs	Monoclonal antibodies
mMRI	Motility Magnetic Resonance imaging
MRE	Magnetic Resonance Enterography
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
PIS	Participant Information Sheet

Glossary

Adalimumab (ADA)	is a human monoclonal antibody that binds to Tumour Necrosis Factor Alpha (vide infra) that is used to treat severe Crohn's disease.
Anti-Tumour Necrosis Factor Alpha (anti-TNFα)	drugs are a class of medications that are used to treat severe Crohn's disease. Examples include infliximab and adalimumab.
Anti-Interleukin	drugs are medications that are used to treat severe Crohn's disease; for example, ustekinumab.
Biosimilars	are medical products that are designed to have active properties that are similar to existing authorized medications, such as anti-TNFα agents.
Calprotectin	is a granulocyte protein that is shed into faeces in the presence of bowel inflammation. It can be used to detect inflammatory activity in Crohn's disease.
Capsule Endoscopy	involves a colour camera, battery, light source and transmitter shaped like a large pill being swallowed by the patient. The capsule camera transmits images to sensors placed on the skin of the abdomen. It allows complete examination of the mucosa of the gastrointestinal tract, particularly the small bowel
Cohort study	is a prospective study that follows a group of similar individuals over time that differ with respect to certain factors under study, to determine how these factors affect rates of a certain outcome.
Colonoscopy	is the examination of the mucosa of the large bowel and the distal part of the small bowel (terminal ileum) with a camera on a flexible tube passed through the anus after full laxative preparation of the bowel.
Computed tomography	is a medical imaging technique that involves X-rays to reconstruct cross-sectional "slices" though the body that can be used to diagnose and characterise many conditions, including Crohn's Disease
C-Reactive Protein (CRP)	is a protein found in the blood, the levels of which rise in response to inflammation
Diffusion weighted imaging	involves a specific **Magnetic Resonance Imaging** (vide infra) sequence which detects the movement of water in tissues. These are often abnormal in inflammatory conditions of the bowel, such as Crohn's disease.
Endoscopy	is a generic term for endo-cavity examination of the bowel with an internal camera on a tube. It includes gastroscopy, colonoscopy and flexible sigmoidoscopy.
Fistula	is an abnormal connection or passageway between two epithelium-lined organs or vessels that normally do not connect.
Harvey-Bradshaw Index (HBI)	is a tool used to quantify symptoms of Crohn's disease. It is a simpler version of the Crohn's disease activity index (CDAI) for assessing disease activity in Crohn's disease.
Ileocolonoscopy	is an alternative term for colonoscopy, but implies successful intubation and visualisation of the terminal ileum (the part of the bowel most commonly affected by Crohn's disease).

Inflammatory Bowel Disease (IBD)	is a generic term for a group of conditions giving rise to inflammation in the gastrointestinal tract. Crohn's disease and Ulcerative Colitis are the most common causes of idiopathic inflammatory bowel disease.
Infliximab (IFX)	is a mouse/human chimeric monoclonal antibody directed against TNFα, and is used to treat severe Crohn's disease.
Luminal Stenosis	is an abnormal narrowing in a tubular organ or structure. In the context of Crohn's disease, it is used to describe reduction in calibre of the tube of the gastrointestinal tract.
Magnetic Resonance Imaging (MRI)	is a medical imaging technique used to visualise internal structures of the body in detail by applying magnetic field and radio frequency energy pulses.
Meta-analysis	is a statistical method used to combine the results of several similar scientific studies to provide an overall summary of the results
Monoclonal Antibodies (mAbs)	are a kind of treatment composed of multiple copies of an identical antibody. Antibodies are large proteins that have a specific shape at one end that binds very tightly to a specific diagnostic or therapeutic target.
Motility MRI (mMRI)	uses rapid Magnetic Resonance Imaging techniques to depict and quantify the degree of small bowel motion, which is often abnormal in patients with enteric inflammation, such as in Crohn's disease
Stricture	is an abnormal narrowing of a duct or passage. In the context of Crohn's disease, it describes a fixed narrowing in the lumen of the gastrointestinal tract. See also **luminal stenosis**.
Tumour Necrosis Factor Alpha (TNFα)	is a chemical released by cells of the immune system to help organize and co-ordinate the body's response to inflammation. It has predominantly pro-inflammatory actions (i.e. worsens inflammation), and plays a key role in the pathogenesis of Crohn's disease. Anti-TNFα agents bind to circulating TNFα, thereby preventing it from exerting its pro-inflammatory effect.
Ultrasound	is a medical imaging technique that can generate images of the internal body structures by detecting reflections from high frequency sound waves generated by a dedicated transducer ("probe").

5.0 Introduction

5.1 Background and Rationale

5.1.1 Scale and nature of the problem

Crohn's disease (CD) is a chronic, relapsing and remitting inflammatory disease of the gastrointestinal (GI) tract affecting c.80k people in the UK [3], most of whom are <25yrs at diagnosis. CD has a huge impact on quality of life (QoL) since it can cause decades of ill health. Some patients have mild disease needing little treatment, but 30% require regular hospital care[3] and 50-80% of these will need surgery[4]. 25% and 15% of patients cannot work fully at 1 and 10 years respectively[5], adding financial distress to physical burden[6]. Lifetime treatment costs are £15k-£120k/patient, similar to heart disease on a per-patient basis, and a major financial challenge to the NHS.

Up to 40% of patients suffering from CD will have severe disease requiring treatment with powerful therapeutic agents termed anti-TNFα monoclonal antibodies (mAbs)[7], which are used to control inflammation. Increasingly, these are initiated early in the course of CD, to heal the bowel before irreversible damage can occur – so-called "top-down" therapy. Anti-TNFα mAbs reduce symptoms, hospitalisation and need for surgery [8]. Unfortunately, they are inconvenient to administer (needing injection/infusion), have side-effects in >10%[9] (e.g. infection–occasionally life-threatening[10]) and may increase cancer risk. They are also expensive (c. £10k / patient / annum), accounting for 2/3 of CD healthcare costs [11]. This raises a dilemma; anti-TNFα agents are effective for many, but their costs and side-effects mean they cannot and should not be administered to all – targeting is needed. The same principle applies to newer biological agents such as ustekinumab, which has recently been approved by the National Institute for Health and care Excellence (NICE) for patients with moderate or severe CD refractory to other therapies.

Targeting biological therapy has two main facets. Firstly, the drugs should be targeted at patients most likely to benefit – those destined to develop severe CD. Secondly, after initiation, they should only be continued in patients in whom sustained therapeutic efficacy is likely. 10-40% do not respond initially to anti-TNFα mAbs and a further 20-40% lose response by one year [12,13], meaning many receive costly and potentially toxic treatment for no clinical benefit. A method to identify at an early stage who will and will not respond to treatment would therefore be a major clinical advance – non-responders could be switched to alternative therapy, both reducing costs and improving outcomes. Such assessment and prediction of response to biologic treatment is the aim of this study.

5.1.2 Current methods for response prediction

To date there has been no systematic review and/or meta-analysis of response predictors for biological therapy. However, a narrative position statement by the World Congress of Gastroenterology asserts that several **clinical parameters** are associated with response to therapy [14]. For example, younger patients, those with shorter disease duration, no previous surgery and non-smokers are believed to have higher response rates [15-19].

C-reactive protein (CRP) has the strongest evidence base as a response predictor – patients with elevated CRP are more likely to respond than those with normal levels. In one study, 76% of patients with CRP >5mg/L responded to infliximab (IFX) vs. only 46% of those with normal CRP [20]. Post-hoc analysis of the ACCENT-1 trial showed that a fall in CRP after treatment can predict long term response; 64% of patients with a CRP drop to <5mg/L by 14 weeks ("CRP normalisation") had maintained response at week 54 vs. only 38% of those with persistently elevated CRP[21]. A fundamental limitation of CRP is that not all patients requiring anti-TNFα mAbs have high CRP at baseline (35% had normal CRP in one RCT[21], confirmed by a large UK prospective cohort study,

Personalised Anti-TNF Therapy in Crohn's Disease (PANTS), meaning it has limited value as a predictor in approximately 1/3 of patients.

Faecal calprotectin (FC) is a granulocyte protein shed into faeces by inflamed bowel. Meta-analyses estimate FC has 80-87% sensitivity (Sn) and 68-82% specificity (Sp) for clinical[22] and endoscopic[23] CD activity, and 78% Sn and 73% Sp to predict relapse [24]. However, it is less useful for small bowel (SB) vs. colonic CD (for both activity assessment [25] and relapse prediction[26]), which is important because the most common reason for anti-TNFα therapy is SB disease[9]. Further, its role in predicting long-term response to anti-TNFα mAbs (vs. documenting CD activity) is unclear. A small retrospective study (n=34) found fC <100µg/g post-induction had 67% Sn, 71% Sp to predict 1 year remission [27]. A prospective report of 65 CD patients found poorer accuracy, with fC<130µg/g having only 61% Sn, 48% Sp for 1 year response [28].

Genetic markers and gene expression profiles are emerging as possible predictors of response, but most studies have been small, retrospective and single centre. The PANTS trial is addressing this via a prospective, multicentre cohort study in a NHS setting, with initial findings expected in late 2017.

Drug trough levels identify patients with inadequate dosing; remission rates can be increased from 65% to 88% by increasing IFX dose in patients with low (<3µg/mL) trough levels after induction [29]. In addition, patients who develop antibodies to infliximab also have lower response rates [30,31]. Post-hoc analysis of ACCENT-1[32] reported levels <3.5µg/mL after induction had 64% Sn, 78% Sp for predicting 1 year response. The clinical and cost-effectiveness of these tests in the NHS is currently being studied in the PANTS trial and via the HTA-commissioned Evidence Synthesis call 14/69/03.

In summary, no currently-available test can predict 1 year response to biological therapy with high accuracy; CRP is the best-studied and most widely-used predictor.

5.1.3 The technology under evaluation in the present study

Magnetic resonance imaging (MRI) is well-established as a diagnostic test for CD; systematic review (SR) shows it has diagnostic sensitivity of 78-93% [33,34] and international consensus states it is "ideally suited" for CD imaging, since it is safe, accurate, and well-tolerated [35]. Patients ingest 1-1.5L of oral contrast agent (e.g. 2.5% mannitol over 40 minutes) to distend the bowel prior to scanning, which employs a variety of sequences to interrogate the GI tract and typically lasts 30mins. MRI is widely disseminated in the NHS for diagnosis and staging of CD, with over 30,000 examinations occurring per annum in England alone. The role of MRI in assessing response to biological treatments is less established.

MRI interpretation by radiologists conventionally relies on morphological observations of bowel wall thickness, wall oedema (estimated using a "fluid sensitive" T2-weighted MRI scan) and increased blood supply (estimated by giving an intravenous contrast agent). These can be combined into subjective MRI activity scores which quantify inflammation and have been validated against endoscopy[36] and/or FC [37]. A limitation of morphological changes is that they lag behind clinical/endoscopic improvement with treatment, limiting utility in response assessment [38] – MRI features do not change immediately even if CD activity has been "switched off". Furthermore, these imaging features are largely subjective, and MRI activity scores are time-consuming and cumbersome to calculate.

An alternative to bowel morphological assessment is quantification of bowel function, specifically peristaltic motion. This can be achieved with MRI by using rapid imaging sequences (motility MRI, mMRI). Patients hold their breath for 15-20 seconds to optimise image quality; by imaging the same location repeatedly during this breath-hold (e.g. every second) it is possible to generate a "cine loop" of moving bowel at that position, exactly as for a film or digital video camera. By repeating this process, moving from front to back, the motion of the entire bowel can be captured in less than 10

minutes (in 8-12 separate breath hold "stacks"). mMRI has potential as a sensitive, rapidly responsive test, as it is a marker of gut function rather than structure. As detailed in section 5.1.4, segmental bowel motility is decreased in active CD, with the degree of this reduction correlating well with the severity of inflammation. Moreover, motility also improves with successful treatment, thereby suggesting it may be able to predict long-term response to biological treatments. Such motion capture "cine" MRI sequences are easily acquired during routine MRI protocols on NHS MRI scanners without need for additional hard- or software; should mMRI have proven utility it could be disseminated rapidly in the NHS.

A further functional tool, based on MRI, is termed diffusion-weighted imaging (DWI)[39]. This uses conventional MRI hardware with specific pulse sequences, sensitive to motion of water molecules in tissues. Inflamed bowel impedes normal water motion, termed "diffusion restriction", helping highlight which parts of the gut are most diseased[40-42]. Single centre data from France (available as a conference abstract only[43]) suggests early improvements in DW-MRI after biological therapy can predict one year remission, but this requires validation in a representative, multicentre cohort.

5.1.4 Current evidence for motility MRI

Motility MRI is both reproducible and sensitive to motility change. A placebo-controlled crossover study [44] found that mMRI was repeatable in volunteers scanned 6 weeks apart (coefficient of variance=4.9%) and highly reproducible between radiologists (intraclass correlation=0.98). A deformation-based technique to quantify the degree of bowel motion (standard deviation of the Jacobian determinant, JacSD; a measure of volume change) was able to depict experimentally-induced motility change by both stimulatory (neostigmine) and inhibitory (buscopan) drugs.

Furthermore, motility changes reflect disease activity in Crohn's disease. In both single-centre retrospective (n=28)[45] and multi-centre prospective (n=96) studies[46], we have shown that segmental SB motility is negatively correlated with histologically-graded inflammation (rho=-0.54). Reduced motility has an 85% Sn and 78% Sp for active CD. Other groups internationally have reported similar data using different metrics to quantify bowel motion. For example, contraction frequency and amplitude correlate with faecal calprotectin [47], and hypomotility and contractile arrest are associated with histopathological presence of Crohn's disease [48].

Regarding demonstration of response to biological treatment, motility improves early after treatment initiation in responders. For example, patients responding to biological agents had significantly improved segmental motility (median=73.4% increase from baseline) vs non-responders (median=25% reduction, $p<0.001$). Improved motility had 92% Sn and 79% Sp for response to treatment in a small (n=46) single centre study[49]. Furthermore, these changes occur rapidly, and are durable - in a cohort of 31 patients who had been imaged at a mean of 16 weeks after anti-TNFα treatment initiation and were then followed up to a mean of 45 weeks of treatment, responders had significantly greater motility changes (median=83.3% rise from baseline) than non-responders (median=22.7% drop, $p<0.001$)[50]. Stable or improved motility at 16 weeks had 93% Sn and 83% Sp for predicting longer term response at 45 weeks[50], suggesting that such early mMRI changes might indeed have clinical utility as a predictor of response to therapy.

5.1.5 Ultrasound as an alternative to MRI

Although MRI is accurate and well-tolerated, it is not the only imaging technique that can be employed for CD imaging[35]. Ultrasound (US) of the bowel has several advantages – it is fast (15 minutes), cheap (NHS tariff £55 vs. £209), radiation-free, non-claustrophobic and does not require intravenous or oral contrast administration. Furthermore, most patients prefer it – preliminary data from a UK multicentre prospective trial suggest around 75% preferred US to MRI. Several meta-analyses suggest that US has similar diagnostic sensitivity to MRI[34,51,52]. A recent multicentre

prospective cohort study showed US was equally effective at identifying the presence of CD as MRI (but was slightly less sensitive for identifying its precise location). However, where CD is already known to be present, and instead the clinical question revolves around prediction of response to therapy, the rapidity and convenience of US may be of particular value. Presently, its utility in this setting is unknown.

5.2 Objectives

5.2.1 Primary objective

To determine whether segmental small bowel motility measurements using motility MRI (mMRI) are able to improve prediction of therapeutic response at one year in patients commencing eligible biological therapy for SB Crohn's disease in comparison to plasma CRP.

5.2.2 Secondary objectives

- To compare predictive ability for therapeutic response at one year between mMRI and faecal calprotectin (FC)
- To compare predictive ability of mMRI, CRP and FC for patient-reported outcome measures (PROMs)
- To identify the optimal threshold for motility changes as a predictive test for response to therapy
- To estimate the intra-observer and inter-observer variability of mMRI, including quality assurance of mMRI hardware, acquisition protocols and post-processing
- To estimate the predictive capability of mMRI in patient subgroups with (i) raised CRP prior to treatment, (ii) non-obstructing stricturing disease, (iii) previous surgery and (iv) those who are receiving anti-TNFα therapy for the first time (i.e. biologic naïve).
- To explore whether response to anti-TNFα or anti-interleukin therapy causes measurable (a) reduction in fasting gut peptide and inflammatory cytokine levels and (b) increase in global SB motility variance, and if there is a relationship to patient abdominal symptoms
- To estimate the predictive ability of DW-MRI for therapeutic response at one year

5.3 Study Design

This is a multisite, prospective cohort study comparing the accuracy of mMRI and CRP in the prediction of response to anti-TNFα and anti-interleukin agents at one year. The study framework is to detect superiority of mMRI over CRP.

6 Methods

6.1 Site Selection

The study sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

6.1.1 Study Setting

A network of UK NHS hospitals with lead radiologists affiliated to the British Society of Gastrointestinal and Abdominal Radiology (BSGAR). Each site has expertise in MRE and lead gastroenterologists with specific expertise in IBD.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the study, the study team will provide them with a copy of this protocol and an Investigator Site File, in which all study documentation, including Participant Information Sheet and Informed Consent Forms, will be stored.

To participate in the MOTILITY study, investigators and study sites must fulfil a set of criteria that have been agreed by the MOTILITY Study Team and that are defined below.

Study sites meeting eligibility criteria and that are accepted as being suitable to recruit to the study, will be issued with the MOTILITY Investigator Site File documentation to use when applying for Site-Specific Assessment (SSA).

Study site eligibility criteria are as follows:

- NHS hospital setting with staff affiliated to the British Society of Gastrointestinal and Abdominal Radiology (BSG) and the British Society of Gastroenterology (BSG).
- Established IBD practice (>150 patients seen annually).
- Established procedures for commencing and monitoring anti-TNFα and anti-interleukin therapy for Crohn's disease.
- Access to, and experience in, performing and interpreting MRE for IBD (not necessarily mMRI).
- Agreement of the relevant departments to allocate study-specific appointments to perform mMRI, CRP and FC at the time points stipulated by the protocol.
- Agreement of at least 1 participating radiologist and a gastroenterologist to take responsibility for ensuring adherence to the study protocol and Good Clinical Practice; and of the site PI to ensure all required protocols are being followed.
- IBD service core members have agreed to support the study, aid in the identification of eligible patients, comply with the study protocol, and liaise with other members of the MOTILITY clinical research team.
- Agreement of all relevant parties to adhere to study protocols for image acquisition, quality assurance, reporting, blinding, sharing of imaging and other data and reports, and administrative and ethical requirements.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a UCL CCTU Clinical Trial Agreement or an Investigator Agreement to comply with the study protocol (confirming their specific roles and responsibilities relating to the study, and that their site is willing and able to comply with the requirements of the study). This includes confirmation of appropriate qualifications, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site that have been delegated significant study related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the study to enable them to conduct the study properly and safely. Sites will be expected to complete a delegation of responsibilities log and provide staff contact details. The site should have sufficient data management resources to allow prompt data return to UCL CCTU.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Agreement or Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI by the MOTILITY Trial Team. The study manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until a letter for activation has been

issued. The Study Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the study in compliance with the protocol as agreed by the Sponsor, and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the study team at UCL CCTU. A list of activated sites may be obtained from the Study Manager.

6.3 Participants

6.3.1 Target population

The study will focus on patients with Crohn's Disease, who have recently commenced or scheduled to commence biological therapy for active small bowel disease, specifically anti-TNFα or anti-interleukin agents. Definitions of "active disease" will be discussed further in Section 6.3.1.4 and 6.5. However, for the purposes of study eligibility, all adult patients in whom the treating physician believes biological therapy is clinically indicated, and in whom the primary target of therapy includes small bowel disease, will be potentially eligible. Patients will be eligible regardless of whether or not they have received prior biological therapy, including prior use of anti-TNFα treatment, anti-integrins (e.g. vedolizumab) or cytokine blockers (e.g. ustekinumab).

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of recruitment. Questions about eligibility criteria should be addressed PRIOR to attempting to recruit the participant.

The eligibility criteria for this study have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the study for their safety and to ensure that the study results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this study if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

- Patients aged 16yrs or more with active luminal small bowel Crohn's disease, with or without colonic disease
- Disease distribution and activity documented by ileocolonoscopy or (for patients with endoscopically-inaccessible disease) magnetic resonance enterography (MRE), enteric ultrasound (US), computed tomography (CT), barium fluoroscopic follow-through (BaFT) or video capsule endoscopy (VCE) performed as part of usual clinical care within the previous 90 daysprior to starting eligible biological therapy or within 14 days after first treatment dose.
- Commenced or scheduled to commence or recommence eligible biological treatment (including biosimilars); specifically, anti-TNF and anti-interleukin agents. If commenced treatment, consent should be obtained within 14 days of first treatment dose if motility sequences are not done as part of standard of care scan.
- The primary target of therapy, in the opinion of the treating physician, is small bowel disease (with or without treatment of concomitant colonic disease).

We will permit baseline assessment of disease activity and distribution to have occurred no more than 90 days before first treatment dose or within 14 days after first treatment dose

6.3.1.3 Participant Exclusion Criteria

- Biological therapies other than anti-TNFα and anti-interleukin agents, such as anti-integrin therapy (e.g. vedolizumab)
- Primary target of therapy is only colonic or perianal fistulising disease
- mMRI contraindicated (e.g. MRI-incompatible cardiac pacemaker, unable to lie flat, pregnancy)
- Any psychiatric or other disorder precluding informed consent
- Small bowel surgery within the preceding 90 days
- Small bowel stricture causing upstream dilatation on imaging or endoscopy (defined as a >50% increase in diameter in comparison to the adjacent small bowel 20cm segment)

6.3.1.4 Definitions of active luminal disease

Since the MOTILITY study will recruit patients with active small bowel disease, and the primary endpoint will be defined by response to therapy, this mandates a robust method to defining disease activity and its improvement (or otherwise) after biological treatment. The definition of "active" disease varies in both clinical practice and the research literature. Although NICE guidance uses the Crohn's Disease Activity Index (CDAI) or its simpler cousin the Harvey Bradshaw Index (HBI), both clinical practice and the research literature have moved towards more objective markers of active inflammation. Similarly, since the aim of the study is to predict response to biological therapy, we require a means of defining such response.

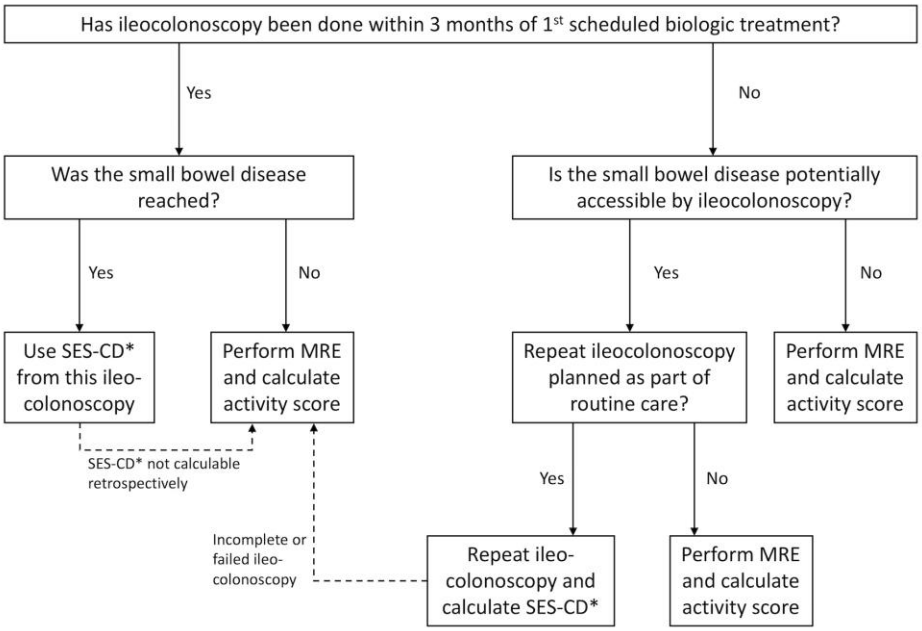
Ileocolonoscopy is the most robust standard of reference for quantifying and monitoring the activity of Crohn's disease, and so is often undertaken prior to initiation of biological treatment as part of standard clinical care. This study will mirror NHS clinical practice, and therefore use ileocolonoscopy wherever possible to define disease activity and monitor response to therapy. **Although there is no mandated minimum endoscopic activity score to permit study entry, patients should have endoscopic stigmata of active small bowel disease sufficient to indicate starting, restarting or a change in anti-TNFα therapy, in the opinion of their treating clinical team**. This clinically-indicated ileocolonoscopic assessment should have occurred within 90 days prior to start of biological treatment or 14 days after first treatment dose, if these endoscopic data are to be used in the MOTILITY study. Such an approach mirrors how biological therapy is used in standard NHS clinical practice.

However, for some patients, it will not be possible to document their disease activity at baseline or assess the response to biological therapy using ileocolonoscopy because they have endoscopically-inaccessible disease (for example, in the proximal small bowel upstream of the terminal ileum, disease upstream of an impassable stricture, or after failed intubation of the terminal ileum); or because ileocolonoscopy is not required as part of standard care. Such individuals will be eligible if they have undergone standard imaging investigations (detailed above) or capsule endoscopy within the preceding 90 days prior to start of treatment, documenting active small bowel disease. To permit standardisation of disease documentation in such cases, these individuals will have a standard morphological MRE appended to their first motility MRI scan within 14 days after first treatment dose, permitting quantitation of disease activity, via MRE activity scores (see section 6.5.1). This morphological MRE need not be repeated for those who have already had MR confirming active disease within 90 days prior to start of treatment, but will be necessary where, for example, study eligibility has been shown by ultrasound or CT – the MRE will then serve as the means by which disease burden can be quantified. For patients who have not undergone disease assessment by imaging or endoscopy within 90 days, but nonetheless have a high likelihood of active small bowel disease based on clinical symptoms and prior documentation of small bowel involvement, and are otherwise eligible for the study, we will permit initial patient consent and baseline visit one assessments (including the research MRI scan, to include both morphological and motility MRI

sequences) to confirm and document disease activity. If this baseline MRI shows no active small bowel disease, then the patient will not be registered on the study.

Although there are no mandated disease activity scores on imaging or VCE to permit study entry, patients should have stigmata of active small bowel disease sufficient to indicate starting, restarting or a change in biological therapy, in the opinion of their treating clinical team.

The flow chart below shows the decision tree to be followed when assessing baseline disease activity:



*SES-CD refers to the score for the **ileal segment only**.

6.3.1.5 Eligibility Criteria for Acquisition and Interpretation of MRI Images

Sites must have access to suitable MRI hard- and software permitting acquisition of the mMRI imaging protocol. The quantification of mMRI images will be undertaken centrally at UCLH, by one of a pool of radiologists with a declared interest in gastrointestinal radiology and experience of >100 enteric MRE studies. Radiologists will hold the FRCR and, if not consultant level, must have undergone 6 months of sub-speciality training in gastrointestinal radiology. Measurement of MRE activity scores will be by radiologists with the same background level of expertise as above, supplemented by specific training in use of the activity score by the study team. Site radiologists will be required to review study MRI scans for urgent unsuspected pathology as a safety requirement. These results will not be used to inform any study endpoints, therefore we will not stipulate specific training or expertise requirements, but radiologists must be deemed competent to identify such unsuspected pathology by the site lead radiologist or their delegate.

6.3.1.6 Co-enrolment Guidance

Patients will be potentially eligible for the MOTILITY study even if recruited into another study, so long as they remain on their biological therapy. By definition, we will be studying patients commencing eligible biologics – patients receiving other novel agents and therapies in a trial setting will be potentially eligible, with prior agreement by the CI, as co-administration of additional immunomodulators alongside biologics is common practice (e.g. azathioprine or methotrexate). CI agreement should be sought prior to co-enrolment.

6.3.1.7 Screening Procedures and Pre-recruitment Investigations

Written informed consent to enter the study must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the study and **BEFORE** any study-specific procedures are performed or any blood is taken for the study. The only procedures that may be performed before obtaining written informed consent are those that would be performed on all patients in the same situation as usual standard of care. However, to avoid unnecessary duplication, inconvenience and risk to participants, where protocol-specified procedures have **already occurred** as part of routine care, these will not be repeated and instead the results from the clinically-arranged procedure will be used (for example, ileocolonoscopy).

6.3.1.8 Biologic treatment and dose optimisation

There will be no change to normal clinical treatment as part of this study. Participants will be treated with a biologic agent, the choice of which will be at the discretion of the treating physician. This includes biosimilar anti-TNFα agents (e.g. Remsima®, Celltrion Healthcare, a biosimilar agent to Remicade®, Merck & Co, both of which are examples of infliximab). Recruitment sites will follow their standard practice for induction and maintenance of patients on biologics. Similarly, dose monitoring and subsequent adjustment/optimisation (for example, measurement of antibodies directed against anti-TNFα agents for those patients starting such therapies) will be as per individual sites' routine clinical practice.

6.4 Comparators

This is a non-randomised prospective cohort study comparing mMRI against CRP (primary) and faecal calprotectin (secondary). All patients will undergo all three tests (see sections 6.4.1 to 6.4.3 below). Recruited patients will also have undergone other tests (imaging, blood tests, colonoscopy etc.) prior to recruitment.

All investigations undertaken as part of normal clinical care will be performed and interpreted by the usual practitioners employed at the recruitment site. Clinical reports will be produced as per standard practice and will be freely available on hospital informatics systems (e.g. Picture Archiving and Communications Systems (PACS); Radiology Information Systems (RIS); Electronic Patient Records (EPR) etc.). Patient consent will be obtained for the research team to access relevant data acquired as part of routine care.

6.4.1 Magnetic resonance imaging

6.4.1.1 Hardware

Recruited patients will undergo mMRI at their recruitment site. The examination will be performed by the usual site radiography team once deemed competent by the site radiology lead. The specific MRI platform used (i.e. manufacturer and field strength) will be at the discretion of the local radiology lead according to scanner availability and usual clinical practice. A minimum field strength of 1.5 Tesla is required; higher field strengths will be permissible.

6.4.1.2 Minimum sequence parameters and quality assurance

The mMRI technique is robust to specific sequence parameters within broad limits. Exact imaging parameters will vary according to the MRI platform being used, but a minimum data set of sequences will be acquired as per the Imaging Manual, which will be provided by the UCL CCTU.

All patients will require oral contrast medium, the nature of which will be at the discretion of the recruitment site and will usually be that used for their standard clinical MR enterography protocol. Patients will be provided with between 1.0 and 2.0L of oral contrast agent, to be ingested over a 40-60 minute period prior to the scan. Wherever possible the volume ingested will be recorded. Patients will be advised to fast for a minimum of 4 hours prior to mMRI and refrain from taking

either pro- or anti-kinetic agents within 24 hours of the scan, including caffeine and nicotine-based products.

In some patients, MRE will have been performed as part of usual clinical care prior to recruitment. As long as the MRE has been acquired no more than 90 days prior to starting the eligible biologic therapy or within 14 days after treatment start and according to the minimum dataset of sequences (further details in guidance documents), the MRE will be eligible for inclusion in the study and will not need to be repeated. Quality assurance and support during setup will be provided by the central study team and Motilent, who will ensure that imaging data can be analysed correctly by their software prior to the first patient being recruited at a given site.

Wherever possible all mMRI scans performed as part of the study will be at the same time of day (i.e. morning or afternoon) for a particular recruited patient

6.4.1.3 Interpretation and blinding

All mMRI scans will be transferred electronically for central interpretation to inform the study endpoints (see 6.4.1.5 below). Quantitation of mMRI motility values is semi-automated but requires a trained interpreter to delineate a suitable region of interest (ROI) of abnormal bowel. This will be conducted by an experienced radiologist (see details in 6.3.1.5 above). ROIs will be placed on the single region of small bowel with the greatest wall thickness on the anatomical planning images. All mMRI scans will be measured by two central readers; the first read (rotating on a weekly basis) will be to inform study primary endpoints and the second read will be used to measure inter-observer variability in the mMRI-derived measurements of small bowel motility (see Section 6.77.1). Central radiologists will be blinded to all clinical information at the time of ROI placement. Sites will also be blinded to the mMRI-derived measurements of small bowel motility to avoid knowledge of the mMRI result from biasing clinical care.

All mMRI scans will also be analysed to examine the relationship between body composition and response to biologic agents (see 6.4.1.7) as a secondary study outcome, and a subset will be analysed to calculate the inter- and intra-observer variability of mMRI as a further secondary outcome (see 6.4.1.6). These interpretations will occur independently of the mMRI measurements used for the main study.

6.4.1.4 Notification of urgent unsuspected pathology

Although recruitment sites will be blinded to mMRI results, local site radiologists will review the images for important unsuspected findings that should be reported to clinical teams for ethical and patient safety reasons. These will include abscesses requiring urgent drainage, bowel obstruction, perforation, deep venous thrombosis, malignancy, or any other serious pathology that the interpreting radiologist judges to require urgent clinical intervention. A log of such urgent and unsuspected notifications will be kept by each recruitment site, with details of the reason for notification.

6.4.1.5 Central collection of study imaging data

Recruitment sites will send the full MRE datasets pseudoanonymised with the study number only (compliant with local data protection rules) using Motilent's cloud-based viewing and mMRI quantitation software portal, if available Motilent servers are ISO 27001 compliant and will reject incorrectly pseudoanonymised data. If the software portal is not available, or recruitment sites prefer, they will also be permitted to transfer images for central review using CD or DVD by posting anonymised discs to the CCTU, clearly marked for the attention of the Chief Investigator [further details will be provided by the CCTU]. As a further alternative, anonymised scans may be uploaded to the UCL secure portal (UCL Data Safe Haven) after receiving relevant training and with the agreement of the UCL CCTU.

6.4.1.6 Measurement of inter- and intra-observer variability of mMRI interpretation

Variability of the interpretation of mMRI will be an important factor affecting the likelihood of its clinical adoption. Preliminary data suggest inter-observer agreement is good[49], but this requires confirmation in a larger, multi-site cohort.

All mMRI scans will be scored by a minimum of two expert radiologists at the central UCL site; the first read will inform the main study endpoints and the second read will be used to calculate interobserver variability (i.e. between readers). These same expert radiologists will additionally re-measure a sample of 52 randomly selected mMRI studies after a washout period of >6 weeks, to estimate intra-observer (i.e. within reader) variability. A further 30 randomly selected cases will be interpreted by 5 site radiologists to estimate inter-observer agreement between gastrointestinal radiologists who are expert in MRE but not familiar with mMRI specifically. These 5 site radiologists will be derived from a selection of recruitment sites but need not all be from different sites. It is possible for readers to disagree fairly considerably regarding the magnitude of motility change, but nonetheless predict the same clinical outcome (for example, if two readers both document a motility improvement), the magnitude of this improvement does not affect the fact the test result, for both readers, is positive – MRI-measured motility suggests that response to biological therapy is likely. Therefore, both numerical agreement (i.e. treating motility as a continuous variable) and overall test agreement (i.e. treating the test outcome as a binary variable) will be calculated. Please see Section 6.14.2 for sample size calculation and Section 6.13.4.2.2 (secondary outcome #7) for outline analysis plan.

6.4.1.7 MRI measures of body composition and therapeutic response to anti-TNFα agents

6.4.1.7.1 Background

Patients with IBD have altered quantities of fat and muscle throughout their body in comparison to unaffected individuals [53-55]. This may be due to many factors including malnutrition, catabolic status and malabsorption, all of which may alter body composition [56,57]. Decreased muscle mass (myopenia) can be demonstrated in many patients with Crohn's disease, even in clinical remission [53]. Furthermore, deleterious body composition alterations in Crohn's patients requiring surgery are associated with higher rates of post-operative complications [58,59]. Regarding anti-TNFα therapy specifically, body composition affects the volume of distribution of many medications, and it is therefore plausible that this contributes to pharmacokinetic failure of anti-TNFα therapy due to inadequate dosing[60]. Initial work from a single-site retrospective cohort has shown that myopenia is associated with non-response to anti-TNFα therapy[61], but this requires verification in a prospective, multicentre setting using robust definitions of response to therapy.

6.4.1.7.2 Hypotheses

1. Myopenia prior to initiation of biological therapy is associated with non-response to treatment.
2. Low muscle:fat ratio prior to initiation of biological therapy is associated with non-response to treatment.

6.4.1.7.3 Data collection

All patients enrolled in the main study will automatically have their data analysed for this secondary outcome; no additional interventions are required. The relevant data will be collected by post-processing and specific analysis of the MRI scans acquired as part of the main study. Similarly, the endpoint for this study is response / remission vs. non-response to biological treatment at one year, and therefore will use the same definitions as for the main study. We will collate data regarding

therapeutic drug trough levels and anti-drug antibody levels only where it has been performed as part of routine clinical care; no additional blood sampling for such levels will be undertaken.

6.4.1.7.4 MRI body composition analysis

MRI scans will be analysed using validated software (Slice-O-Matic version 4.3, Tomovision, Montreal, Canada). Total skeletal muscle and adipose tissue surface area will be measured in cm^2 using a single axial T2 weighted image at the level of the L3 vertebral body. Areas will be normalised for height in metres squared and reported as the lumbar skeletal muscle and adipose tissue index in cm^2/m^2. Myopenia will be defined using cohort-specific cutoffs as defined by the lowest quartile.[62].

6.4.1.7.5 Sample size and analysis plan

See Section 6.14.2 (sample size) and Section 6.15(secondary outcome #10) for outline analysis plan.

6.4.2 C-reactive protein (CRP)

Plasma samples for CRP will be taken according to normal local practice, and will be measured by the relevant recruitment site's biochemistry laboratory. Since CRP measurements are routinely available in standard practice, these results will not be withheld from clinical teams.

6.4.3 Faecal calprotectin (FC)

Stool sample testing kits for FC measurement will be provided for each participant with an addressed return envelope. To ensure reproducibility of the FC result, all samples will be processed by the same laboratory (Royal Devon and Exeter). Results will not routinely be returned to study teams unless the FC would have been requested as part of routine clinical care.

In the event of patients not returning samples to the central laboratory for analysis, clinical FC results (if available) will be collected from sites.

6.5 Documentation and assessment of disease activity

6.5.1 Baseline assessment

Tests performed as part of standard clinical care will be used to confirm and document the presence of active small bowel disease. These will also serve as a baseline standard to permit later assessment of response or otherwise to biological therapy. As documented in section 6.3.1.4 above, ileocolonoscopy will be the default standard of reference for disease activity. The means of assessing Crohn's disease activity will be the Simple Endoscopic Score for Crohn's Disease (SES-CD)[63]. This is the preferred metric of the International Organisation for the study of Inflammatory Bowel Disease (IOIBD)[64]. If ileocolonoscopy is not possible, has not occurred (or is not planned) as part of standard clinical care, or would not reach the involved segment of bowel, MRE will be substituted as an alternative objective measure of disease activity (see flow chart in section 6.3.1.4). The SES-CD will be scored by site gastroenterologists, using photographic documentation wherever possible.

The scores will be assigned for the **terminal ileal segment only**, using the table below:

Variable	**Score**			
	0	**1**	**2**	**3**
Ulcer size	None	Aphthous ulcers (0.1 to 0.5cm)	Large ulcers (0.5 to 2.0cm)	Very large ulcers (>2.0cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected	<50%	50-75%	>75%

Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

MRE will be evaluated by central radiologists, blinded to all clinical information, using an activity index that has been validated against histopathological activity scores[65] and the Crohn's Disease Endoscopic Index of Severity (CDEIS) [VIGOR++ study investigators, personal communication]. This MRE score will be calculated for the segment of bowel with the greatest mural thickness on anatomical HASTE (or equivalent) images, and will be defined as follows:

Activity score = 1.79 + 1.34*mural thickness score + 0.94*mural T2 signal score

The mural thickness and T2 signal scores will be defined as follows:

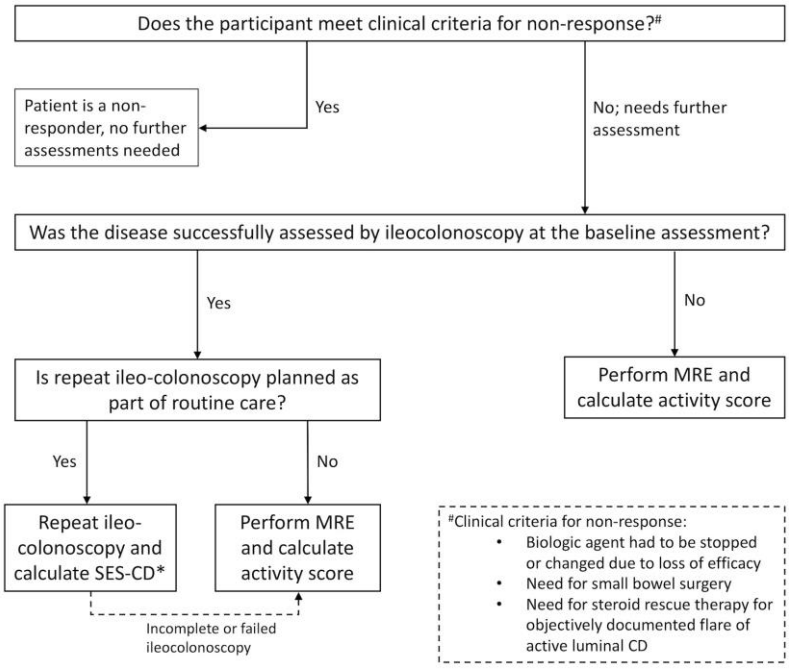
Score	Mural thickness	Mural T2 signal
0	0-3mm	Equivalent to normal bowel wall
1	>3-5mm	Minor increase in signal – bowel appears dark grey on fat saturated images
2	>5-7mm	Moderate increase in signal – bowel appears light grey on fat saturated images
3	>7mm	Marked increase in signal – bowel wall contains areas of white high signal approaching that of luminal content

6.5.2 Therapeutic response assessment at one-year follow-up

Disease response assessment after one year of biological therapy will also be assessed using ileocolonoscopy wherever possible, supplemented by MRE activity scores where appropriate. These tests must be completed within 18 months of the patient's first biologic treatment in the study. The only exceptions to these requirements will be where clinical parameters have already made it clear that the participant has not responded to biologics, which will be if any of the following conditions are met:

- The biologic agent had to be stopped or changed because, in the opinion of the treating clinician, there has been loss of efficacy
- Enteric surgery required for the target small bowel disease
- Steroid rescue treatment required for a flare of active luminal Crohn's disease. This will be defined as a clinical presentation that, in the opinion of the treating physician, is due to active luminal Crohn's, confirmed by at least one objective test documenting inflammation (including biochemical, imaging or endoscopic indices).

The following decision tree will be followed:

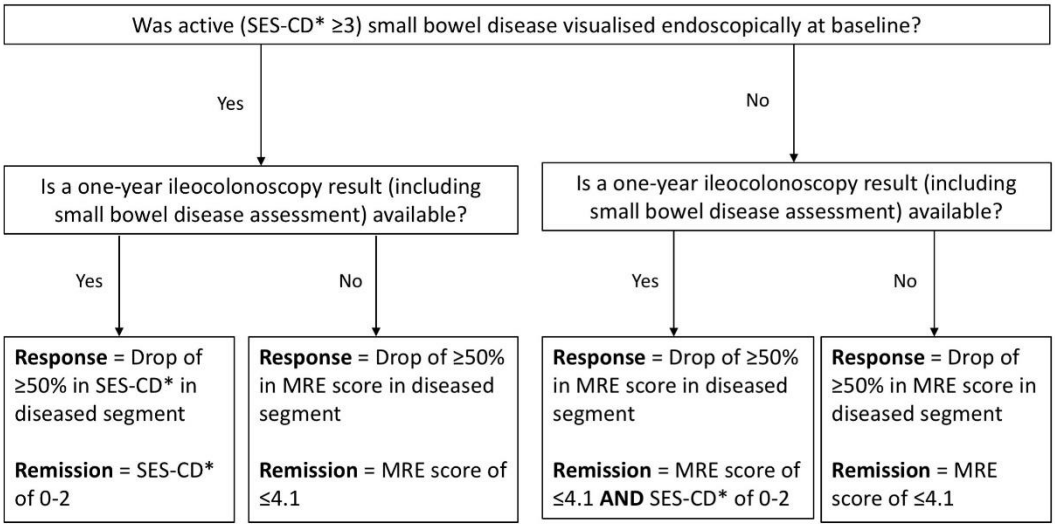


*SES-CD score refers to the **ileal segment only**.

The SES-CD and the MRE activity scores will be calculated in the same manner as for the baseline assessment detailed in section 6.5.1. Where possible, endoscopic definitions of response and remission will be prioritised; for this to be possible, patients must have undergone ileocolonoscopy at both baseline and follow-up, as the only acceptable means of defining response is a change in SES-CD from baseline[64]. Some participants will have successful ileocolonoscopy, but will have disease that is not amenable to endoscopic assessment (e.g. proximal small bowel disease, impassable stricture); these patients will be assessed using MRE. If a patient has both endoscopic and MRE assessments of their disease, the endoscopic assessment will serve as the reference standard of disease activity and therapeutic response, unless the endoscopically-evaluated segment showed no active Crohn's disease (SES-CD 0-2) at baseline.

If a participant has ileocolonoscopy** at 12-18 month follow-up, but not at baseline, this can be used as supporting information to help confirm or refute the possibility of remission (e.g. remission is impossible if the SES-CD is 3 or more), but cannot be used to define response in the absence of a baseline SES-CD measurement.

Response and remission will therefore be defined as below:



*SES-CD refers to the score for the **ileal segment only**.

**Ileocolonoscopy may be up to 18 months in line with protocol v6.0 updates

6.6 Patient-Reported Outcome Measures

Prediction of gut inflammation, while important, is only one facet of adequate control of Crohn's disease. An ideal test would also predict improvements in patient symptoms and quality of life. Although objective measures of biological inflammatory activity (such as those emphasised in section 6.5) are correlated with symptoms, this association is not absolute. Therefore, various quality of life (QoL) scores will also be collated and used to inform study secondary outcomes.

6.6.1 Overall quality of life

The European Quality of Life score, five dimension, five level version (EQ-5D-5L) will be used to document and quantify overall QoL, as recommended by NICE. This is a descriptive system of health-related QoL that relies on self-reported scores across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension is scored by the participant at one of five levels of severity (no problems, slight problems, moderate problems, severe problems and extreme problems). This is supplemented by a visual analogue scale (VAS) for the individual's self-rated overall health-related QoL. The health state derived from the descriptive five dimension, five level component of the instrument will be converted to a summary index using the English value set. We will define an increase of 0.076 points as representing a clinically important improvement [66].

6.6.2 Disease-specific measures

6.6.2.1 Crohn's and Ulcerative Colitis Questionnaire, 8 item

Crohn's disease-specific measures of severity will also be recorded. To promote comparability with the UK Inflammatory Bowel Diseases Biologics Registry, the Crohn's and Ulcerative Colitis Questionnaire, 8 item version (CUCQ-8) will be used [67]. This consists of eight questions regarding patient symptoms over the immediately preceding two weeks, and includes the following aspects; tiredness, impact on social trips out, feeling generally unwell, abdominal pain, nocturnal bowel movements, abdominal bloating, feeling upset, and need to rush to the toilet. The minimum clinically important improvement of the CUCQ-8 is not yet known with certainty (Dr Laith Alrubaiy, personal communication), but will provisionally be defined as a change of 9 points or more.

Question	Possible responses
On how many days over the last two weeks have you felt tired	0-14 days
In the last two weeks did your bowel condition prevent you from going out socially?	No, not at all Yes, some of the time Yes, most of the time Yes, all of the time
On how many days over the last two weeks have you felt generally unwell?	0-14 days
On how many days over the last two weeks have you felt pain in your abdomen	0-14 days
On how many nights in the last two weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed?	0-14 nights
On how many days over the last two weeks has your abdomen felt bloated?	0-14 days
In the last two weeks, have you felt upset?	No, not at all Yes, some of the time Yes, most of the time Yes, all of the time

On how many days over the last two weeks have you had to rush to the toilet?	0-14 days
If you did not complete any of these questions, please record the question number(s) below and, if possible, give a reason why it was not completed	

6.6.2.2 IBD-Control 8 item

A second PROM will also be used, the IBD-Control 8 item instrument[68], which includes not only symptom-based components but also a patient-judged assessment of whether or not their disease is under good control, both by using yes/not sure/no questions and with a visual analogue scale (VAS). The minimal clinically significant change will be 4 points for the IBD-Control 8 and 20 points for the IBD-Control VAS, subject to change following ongoing validation work (Dr Keith Bodger, personal communication).

The original form of the IBD-Control instrument will be reproduced as a study CRF, and comprises the elements below:

Question	Possible responses
Do you believe that your IBD has been well controlled in the past 2 weeks?	Yes / No / Not sure
Do you believe that your current treatment is useful in controlling your IBD?	Yes / No / Not sure
Over the past 2 weeks, have your bowel symptoms been getting better, getting worse or not changed?	Better / No change / Worse
In the past 2 weeks, did you miss any planned activities because of IBD?	Yes / No / Not sure
In the past 2 weeks, did you wake up at night because of symptoms of IBD?	Yes / No / Not sure
In the past 2 weeks, did you suffer from significant pain or discomfort?	Yes / No / Not sure
In the past 2 weeks, did you often feel lacking in energy (fatigued)?	Yes / No / Not sure
In the past 2 weeks, did you feel anxious or depressed because of your IBD?	Yes / No / Not sure
In the past 2 weeks, did you think you need a change to your treatment?	Yes / No / Not sure
How would you rate the overall control of your IBD in the past two weeks?	Vertical line marked on the scale
Worst possible control	 Best possible

6.6.2.3 Harvey Bradshaw Index

Although not technically a patient-reported outcome measure, the Harvey Bradshaw Index (HBI) is a commonly-used clinical scoring tool that encompasses patient-scored elements[69] as well as findings on physical examination. The HBI is commonly calculated at routine outpatient visits and well-recognised and understood by gastroenterologists. Therefore, to promote comparison with other studies and national audits (e.g. the National Biologics Audit), we will collect HBI where it has been calculated in routine practice but will not specifically mandate that it is measured.

The HBI is reproduced for reference below:

	Item	Possible responses
Patient to complete	A. General wellbeing (scored for the previous day)	0 = very well 1 = slightly below par 2 = poor 3 = very poor 4 = terrible
	B. Abdominal pain (scored for the previous day	0 = none 1 = mild 2 = moderate 3 = severe
	C. Number of liquid stools (scored for the previous day)	Any integer
Physician to complete	D. Abdominal mass	0 = none 1 = dubious 2 = definite 3 = definite and tender
	E. Presence of complications	0 = none 1 point for any of: • Arthralgia • Uveitis • Erythema nodosum • Aphthous ulcers • Pyoderma gangrenosum • Anal fissure • New fistula • Abscess

6.7 Sub-study 1 – mechanisms of dysmotility in Crohn's disease

6.7.1 Background

Motility disturbance in active Crohn's is well documented, but is not simply confined to the actively-inflamed bowel. For example, active SB disease slows gastric emptying[70] and reduces orocaecal transit time[71]. More recently, mMRI measurements show that both patient symptoms and objective inflammatory burden (quantified by calprotectin) are associated with disordered motility across the entire SB (i.e. "global" gut motion)[72]. The magnitude of bowel motion is unaffected, but there is loss of the normal co-ordinated motility seen in healthy bowel (quantified by reduced small bowel motility variance, SbmVar). Therefore, inflammation and symptomatic dysmotility are not always co-localised in the same bowel segment, but the mechanisms by which localised inflammation in CD (for example in the terminal ileum) causes global, panenteric motility disturbance is unknown.

The inflammatory milieu induced by active disease is one possibility; the cytokines IL-1, IL-6 and IL-10 are all affected by active Crohn's [73], and may affect gut motion. For example, IL-1 signalling is required in a murine model of post-operative ileus [74]. Another pro-inflammatory cytokine, IL-6, may also suppress motility; humans with ileus have higher levels of IL-6 than healthy controls[75]. Conversely, IL-10 (a broadly anti-inflammatory mediator) has an opposite effect – IL-10 knockout mice develop a severe, refractory post-operative ileus and exogenous IL-10 speeds its recovery [76]. IL-10 is usually upregulated in active CD [77], and so may serve as a beneficial counterbalance to these

other largely anti-kinetic cytokines. It is therefore highly plausible that these mediators drive the dysregulated gut motility seen in active Crohn's disease.

A second possible mediator is the enteroendocrine cell (EC). EC sense intraluminal nutrients, releasing various peptides and amines to orchestrate gut secretory and motor function. Active inflammation in Crohn's disease disrupts their normal control, likely via cytokine-driven mechanisms since IL-4[78] and IL-6[79] both promote EC upregulation in a murine model of inflammation. In humans, active Crohn's causes 2- to 3-fold increases in ileal expression of glucagon-like peptide-1 (GLP-1)[80] and polypeptide YY (PYY)[81]. PYY is known to delay gastric emptying[82], reduces food intake[83] when given parenterally and slows jejunal motility[84]. GLP-1 also slows gastric emptying[70] and SB motility[85]. Accordingly, their increase in active Crohn's disease is associated with nausea and anorexia – asymptomatic patients in remission have normal EC peptide levels[81].

6.7.2 Hypotheses

The above paragraphs suggest that inflammation underpins elevated cytokine and gut peptide levels, and this, in turn, drives enteric dysmotility. The fundamental principle is that there is a direct reciprocal relationship between these mediators and motility, leading to the hypothesis:

1. Patients who respond to biologic treatment have (a) significantly lower plasma peptide and gut cytokine levels and (b) significantly greater small bowel motility variance (SbmVar) than patients who do not respond
2. Patients with elevated fasting plasma peptide / cytokine levels at follow-up have significantly lower SbmVar than patients with normal levels
3. Patients with greater SbmVar after biological treatment have significantly lower symptom burden than those with low SbmVar.

6.7.3 Recruitment sites and participants

Since measurement of fasting gut peptides requires immediate on-site centrifuging and freezing, only a subset of sites will collect these. All participants at these sites will be potentially eligible for this sub-study; a sample size of 44 patients is required for this sub-study (see Section 6.12.2.4). Additional consent will be requested for this sampling.

6.7.4 Sample collection

Consenting patients will fast overnight prior to mMRI; blood samples will be collected just prior to each mMRI attendance (i.e. baseline, week 12-30 and at one year). Sample collection prior to oral contrast medium ingestion (e. g. mannitol) to prevent influencing gut peptide levels. Participants who have already undergone mMRI prior to study recruitment will be asked to provide a baseline blood sample at a separate visit. Samples will be centrifuged to extract plasma & serum which will be frozen and thereafter sent to the Nottingham Biomedical Research Unit for measurement of GLP-1, PYY, IL-1, IL-6 and IL-10 levels by Enzyme-Linked ImmunoSorbent Assay (ELISA). Samples will be collected and stored according to a Lab manual which will be provided to each site participating in this sub-study.

6.7.5 mMRI analysis

mMRI analysis will be undertaken at the central UCL site as for the main study outcomes; two radiologists will independently draw regions of interest (ROIs) around morphologically normal small bowel, at each time point, as previously described[86]. Motilent will quantify mean small bowel motility (standard deviation of the Jacobian determinant) and its variance.

6.7.6 Documentation of patient symptoms

Participants will already be completing symptom score questionnaires for assessment of the main study outcomes (CUCQ-8, IBD-Control 8 and EQ-5D-5L), which will serve to document patient symptoms of abdominal pain, altered bowel habit and general wellbeing.

6.8 Sub-study 2 – Diffusion-Weighted MRI (DW-MRI) for response prediction

6.8.1 Background

DW-MRI uses conventional MRI hardware but specific pulse sequences to estimate the Brownian motion of water in body tissues[39]. As cell density increases (for example, due to the lymphocytic infiltrate of active inflammation in Crohn's), water motion is impeded, termed diffusion restriction. Fibrosis and cell swelling also contributes to alterations in diffusion signal[87]. Since many of these factors can be beyond the resolution of morphological MRI parameters, DW-MRI can be abnormal when the gut appears structurally normal on conventional sequences[88]. This raises the possibility that, just as for motility MRI, this functional MRI sequence will respond more rapidly to biological treatment than morphological MRI, thereby improving prediction of therapeutic response at one year.

6.8.2 Hypotheses

1. Improved DW-MRI is better able to predict RoR (see 6.5.2) at one year after biological therapy for active SB Crohn's disease than normalisation in CRP.
2. The combination of DW-MRI with motility MRI improves predictive performance of the test for RoR at one year after biological therapy.

6.8.3 Recruitment sites and participants

Since DW-MRI is a widely-available sequence on virtually all modern MRI scanners, all recruitment sites will be able to participate in the DW-MRI sub-study, if desired. However, since it necessarily extends the scanning period by approximately 5-10 minutes (depending on precise scanning parameters and MRI unit), certain individuals may prefer not to participate in this sub-study despite continuing with the main MOTILITY study.

6.8.4 Sequence selection and DW-MRI imaging parameters

The majority of evidence supporting use of DW-MRI in Crohn's disease has used b values of 0 and either 600 or 800 s/mm^2 [40,42,87,89-91], although limited data suggests that higher values (e.g. 1500 s/mm^2) are superior at higher field strengths (e.g. 3.0 Tesla)[92]. We will stipulate a minimum of 600 s/mm^2 for the highest b value acquired, but will permit sites to use higher values in line with their local practice. Details of minimum imaging dataset parameters for DW-MRI are provided in the Imaging Manual. DW-MRI will not require a separate appointment, and instead will be appended to the same MRI examination as for motility MRI.

6.8.5 Image retrieval and analysis

Images will be returned centrally for analysis in the same manner as for the main study. DW-MRI results, as for other imaging, will not be revealed to recruitment sites to avoid biasing treatment trajectory. DW-MRI images will be scored both qualitatively and quantitatively. Unlike mMRI, there is relatively little preliminary data on which to determine at what point an early change in DW-MRI should be regarded as indicative of response to treatment. Single-centre data from repeat DW-MRI after 12 weeks of anti-TNFα therapy, available only as a conference abstract[43], suggest that the best single DW-MRI parameter is an increase in apparent diffusion co-efficient (ADC) of >10%. Therefore, DW-MRI will be interpreted both subjectively (via scoring of the DW-MRI images as follows: 0 = normal, 1 = possibly abnormal, 2 = probably abnormal, 3 = definitely abnormal), and quantitatively, via calculation of ADC using a monoexponential model.

We will also calculate a modified Clermont score[41], a composite of DW-MRI and morphological parameters, as follows:

Score = 1.646 * bowel thickness – 1.321*ADC+5.613*oedema+8.306*ulceration+5.039

The same series as above suggests that a >25% improvement in Clermont score at week 12 best predicts response after 1 year.

6.8.6 Image interpretation and blinding

This will be handled in the same manner as for the motility MRI.

6.10 Protocol Treatment Discontinuation

In consenting to the study, participants are consenting to study treatments, follow-up and data collection. However, an individual's participant may be withdrawn from the study early for any of the following reasons:

- An adverse event which precludes proceeding with study interventions (e.g. MRI)
- Inability to complete a study intervention that is only realised post-consent (e.g. extreme claustrophobia that is not apparent until an attempt at MRI is made)
- Any change in the participant's condition that in the clinician's opinion justifies withdrawal
- Withdrawal of consent by the participant

As participation in the study is entirely voluntary, the patient may choose to discontinue the study at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuation, a reasonable effort should be made to establish this reason and inform the CCTU, whilst remaining fully respectful of the participant's rights.

Participants who discontinue the study, for any of the above reasons, should remain in the study for the purpose of follow up and data analysis only if they have undergone the required interventions to permit study endpoints to be assessed correctly.

6.11 Recruitment and Retention

6.11.1 Recruitment

Patients will be identified by the local clinical PI, Inflammatory Bowel Disease Multidisciplinary Team (MDT) co-ordinator, GI specialist nurse or other suitably trained delegated individual via:

- Endoscopy lists
    - Patients with endoscopically active Crohn's disease who may require commencing on / restarting / change in biological therapy
- Outpatient clinics
    - Patients with clinically active Crohn's disease who are in the process of being assessed for biological therapy
- Hospital inpatients
    - For example, patients with a flare of Crohn's disease who are likely to require subsequent biological therapy
- MDT meetings and discussions
- Requests for small bowel imaging investigations

Each recruitment site will provide specific MRI appointments for MOTILITY study patients.

6.11.2 Screening log

A screening log will be kept at site, documenting all potentially eligible patients who are approached. The reasons for non-recruitment (e.g. patient refusal, contraindication to MRI scanning, patients subsequently deemed ineligible) will be recorded, to ensure the recruited patient cohort is representative of the target population. This log will be requested by the sponsor on a regular basis.

6.11.3 Retention

Patients will be contacted by the relevant recruitment site Research Nurse or delegated individual to remind them of their MRI appointment date and time. They will also receive telephone, email and postal reminders (according to patient preference) to return completed study questionnaires and other materials to the relevant site. Please also see sections 6.11.2 to 6.11.4 regarding loss to follow-up and participant transfers

6.12 Outcomes

Definitions

- **Response or remission (RoR):** response or remission (RoR) to biologic therapy at one year will be defined as per Section 6.5.2 above.
- **Stable or improved MRI-measured segmental small bowel motility**: defined as either unchanged or increased small bowel motility, quantified by the mean of the standard deviation of the Jacobian determinant of pixels within a radiologist-drawn region of interest, between baseline and week 12-30.
- **Normalisation of CRP**: defined as a reduction from ≥5.0mg/L at baseline to <5.0mg/L at week 12-30.
- **Normalisation of faecal calprotectin:** defined as a reduction from ≥100µg/g at baseline to <100µg/g at week 12-30.
- **Clinically significant improvements in quality of life**: from baseline to one year. See section 6.6 for further details of QoL measures.
    - European Quality of Life 5 dimension, 5 level (EQ-5D-5L) score: defined as a 0.076 point improvement
    - Crohn's and Ulcerative Colitis Questionnaire 8 item (CUCQ-8) score, defined as 9 points
    - IBD-Control-8 defined as 4 points
    - IBD-Control-VAS defined as 20 points
- **Myopenia**: defined as patients below the lower quartile of the distribution of skeletal muscle at baseline.
- **Low skeletal muscle:fat ratios**: defined as patients below the lower quartile of the distribution of skeletal muscle:fat ratios at baseline.

For all outcomes, an additional eight weeks will be permitted for study assessments and procedures to be completed after one year has elapsed following the first biological treatment.

6.12.1 Primary Outcome

Difference in sensitivity between stable or improved MRI-measured segmental small bowel motility *versus* normalisation of C-reactive protein at week 12-30 to predict response or remission (RoR) to biologic therapy at one year.

6.12.2 Secondary Outcomes

1. Difference in specificity between stable or improved MRI-measured small bowel motility *versus* normalisation of C-reactive protein at week 12-30 to predict RoR.
2. Difference in area under the receiver operating characteristic curve (ROC AUC) between changes from baseline to the week 12-30 in continuous small bowel motility MR score and in C-reactive protein levels to predict RoR.
3. Difference in prognostic accuracy between changes in the continuous small bowel motility MR score *versus* changes in C-reactive protein levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure (EQ-5D-5L, CUCQ-8 and IBD-Control 8).
4. Difference in (i) sensitivity and (ii) specificity between stable or improved MRI-measured small bowel motility and normalisation of faecal calprotectin at week 12-30 for predicting RoR. Difference in (iii) ROC AUC between changes from baseline to week 12-30 in small bowel motility and in faecal calprotectin for predicting RoR.
5. Difference in prognostic accuracy between changes in the continuous MRI-measured small bowel motility score *versus* changes in faecal calprotectin levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure.
6. Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including MRI-measured small bowel motility *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.
7. Interobserver variability of MRI-measured small bowel motility for (a) experts in mMRI and (b) experienced radiologists without prior mMRI experience. Intraobserver variability of MRI-measured small bowel motility for experts in mMRI.
8. Difference in (a) plasma levels of (i) gut peptides and (ii) inflammatory cytokines and (b) small bowel motility variance between patients with and without RoR.
9. Difference in small bowel motility variance between patients with normal and elevated levels of (a) gut peptides (b) inflammatory cytokines and (c) between patients with and without abdominal symptoms at each time point.
10. Difference in response rates to biological treatment at one year for (a) patients with and without skeletal muscle myopenia and (b) patients with and without low skeletal muscle:fat ratios.
11. Sensitivity and specificity of (a) >10% increase in ADC and (b) >25% reduction in Clermont score between weeks 0 and 20-28 for RoR to biologic therapy at one year.
12. Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including change in ADC value derived from DW-MRI between baseline and week 12-30 *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.
13. Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including the Clermont score derived from DW-MRI *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.
14. Difference in prognostic accuracy between changes in the Clermont score *versus* changes in (i) C-reactive protein and (ii) faecal calprotectin levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure.
15. Incremental prognostic value of DW-MRI parameters in conjunction with motility MRI scores for response to biologic therapy at one year.

6.13 Participant Timeline

6.13.1 Schedule of assessments

A detailed Schedule of Assessments Guideline for the MOTILITY study will be provided to each site by the CCTU. A summary is presented below.

	STUDY PERIOD		
	0 to 4 weeks	12 - 30 weeks	One year (- 8 weeks and + 26 weeks)
Consent and Eligibility			
Study Consent	X		
Medical history/AE check	X	X	X
CLINICAL DATA			
Indication for biological therapy	X		
Need for biological therapy drug levels adjustments		X	X
Need for medication switch		X	X
Need for corticosteroids	X	X	X
Need for surgery	X	X	X
Overall clinical observations	X	X	X
CLINICAL TESTS			
MRI (including motility) [(i)(vii)]	X	X	X
CRP[(i)(vi)]	X	X	
Faecal calprotectin[(i)(viii)]	X	X	X
Ileocolonoscopy[(i),ii)]	X		X
Diffusion weighted MRI[(iii)]	X	X	
QUESTIONNAIRES			
Harvey Bradshaw Index[(iv)]	X	X	X
EQ-5D-5L	X	X	X
CUCQ-8	X	X	X
IBD-Control	X	X	X
GUT PEPTIDES AND CYTOKINES[(v)]			
GLP-1 and PYY	X	X	X
IL-1, IL-6 and IL-10	X	X	X

[(i)]MRI and ileocolonoscopy may have occurred as part of routine clinical care within 90 days prior to start of biological treatment. If these tests have been conducted according to study stipulations (e.g. meeting MRI minimum dataset), they do **not** need to be repeated –

[(ii)]See section 6.5 for circumstances under which ileocolonoscopy is required.

[(iii)]For patients enrolled in the DW-MRI sub-study.

[(iv)]Harvey Bradshaw Index documentation should be recorded if part of routine clinical care, if this is not available this will not be considered a protocol deviation.

[(v)]For participants enrolled in the mechanistic sub-study (*additional consent required*).

(vi) CRP sample collection to be done within 90 days prior to start of treatment or 2 days after first treatment dose.

(vii) Motility sequences if not done as part of Standard of care, should be done within 14 days of starting treatment.

(viii) Faecal calprotectin sample collection to be done within 90 days prior to start of treatment or within 14 days after first treatment dose

6.13.2 Early Discontinuation of Follow-up

If a participant chooses to discontinue the study, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole study, even though they no longer wish to continue with the study interventions (for example, the final MRI scan at one year). If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the study. UCL CCTU should be informed of the withdrawal in writing using the appropriate MOTILITY study documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early. Necessarily, if some participants are unable to contribute to the study endpoints (for example, withdrawing from the study before a one-year therapeutic response definition can be assigned), their data will not be used when calculating the study outcomes that rely on those data points. However, if a participant is willing to undergo some (but not all) of the study interventions, such that response assessment can be achieved (e.g. declining MRE but not ileocolonoscopy, or vice versa), their data will be retained.

Participants who become unable to continue with biologic therapy for reasons other than efficacy (for example, those who develop an allergy to it) will be withdrawn from the study and replaced if this occurs prior to the week 12-30 assessments. If they have already completed the week 12-30 assessments, they will **not** be replaced and instead will be deemed to be biologic non-responders and analysed as part of the primary outcome population.

6.13.3 Participant Transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating study centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

6.13.4 Loss to Follow-up

A patient will be classified as loss to follow-up if a site has been unable to contact the patient and does not know their current status. Loss to follow-up after recruitment and completion of research interventions is relatively unlikely because recruited individuals are managed by well-established IBD teams at all sites. Due to the nature of the disease and the potentially serious side-effects of therapy, patients are monitored closely as part of routine practice. We will replace participants who do not complete the baseline and week 12-30 research assessments, as long as recruitment is still open. Some participants may decline the one year follow up assessments required to inform study endpoints (despite completing the baseline and week 12-30 assessments). Such participants will also be replaced, if recruitment remains open. Patients who cannot be replaced because recruitment has closed, will remain in the study and their data used for secondary outcomes if possible.

6.13.5 Missed visits and assessments

Although sites will make every attempt to ensure participants complete all scheduled assessments, it is possible that some will be overlooked or fail (for example, faecal calprotectin samples may

degrade if not processed rapidly). Although such individuals cannot contribute to the primary outcome, they will not be withdrawn from the study, as their data may still be used to inform the secondary outcomes. Where missed visits or assessments are required only for secondary study outcomes, no additional recruitment will be conducted. Participant data will be retained to inform all relevant secondary outcomes. Where these missed visits or assessments are required to inform the primary outcome (i.e. mMRI and CRP), an additional participant will be recruited if recruitment is still open.

6.13.6 Study Closure

For regulatory purposes, the end of the main study will be after the final reference standard definition response to therapy assessment has been completed for the last recruited patient (last patient last visit) and all data queries closed. At this point, the "declaration of end of study" form will be submitted to the requisite ethical and governance committees. However, we will request that participants give their consent to permit access to their routinely-held clinical data for an additional 4 year period of follow-up (i.e. total of 5 years), with no further research interventions.

6.14 Sample Size

The number of evaluable participants required is 140. We initially calculated a target sample size of 200 to allow for up to 30% rate of attrition. The total number of participants that can be recruited has been increased to a maximum of 240 until May 2022, due to the impact of Covid-19 pandemic on the study in addition to existing protocol deviations and withdrawals. This rate was quantified using accumulating data from the first year of recruitment, which showed that a higher than anticipated number of patients either did not undergo the required assessments within the correct timelines, or declined to attend such assessments. This will ensure that the number of evaluable patients contributing data to the primary analysis is maximised.

6.14.1 Primary power

Power is based on the primary outcome i.e. the comparison between the sensitivity of stable or improved mMRI-measured segmental small bowel motility (intervention) vs. normalisation of CRP (comparator) at week 12-30 compared to baseline to predict response/remission to biologic therapy at one year:

- Paired design; both tests for all patients; per-patient unit of analysis
- Positive tests defined as per Section 6.10.1 (mMRI; SB motility at 12-30 weeks equal to or greater than baseline; CRP: reduction from ≥5mg/L at baseline to <5mg/L at 12-30 weeks).
- Sample size calculation method: Two-sample paired proportions (McNemar) test[95].

6.14.1.1 Assumptions

6.14.1.1.1 Test sensitivities

Sn of CRP normalisation for DRR is 40%, calculated as follows from ref [21]):

1. 65% of patients will have raised CRP at baseline
2. CRP normalisation occurs in 113/207=55% of those with initially raised CRP (Table 2 of ref [21]).
3. Hence, 65*55=36% of all patients will have "CRP normalisation".
4. Of patients with CRP normalisation, 56.6% had maintained response at 1 year, i.e. 20.2% of all patients (Table 2 of ref [21]).
5. Prevalence of 1 year response or remission is 78/156=50% (Table 4 of ref [21]) in biologic-naïve patients.
6. Prevalence of 1 year response or remission may to be up to 20% lower in the non biologic-naïve.

This permits the following 2x2 contingency table, populated with 100 hypothetical patients:

	Response status at 1 year		Total
	Response	No response	
CRP normalised	20 [from (4) above]	16	36 [from (3) above]
CRP not normalised	30	34	64 [from (3) above]
Total	50 [from (5) above]	50 [from (5) above]	100

Sensitivity of CRP normalisation for response is therefore 20/50 (light grey cells above) = 40%.

Data for mMRI suggest it may be up to 90% sensitive for early response but there are fewer data for DRR. Accordingly, the power calculation is based on a more conservative 60% (i.e. 20% difference between tests, which would nonetheless be clinically important).

6.14.1.1.2 Prevalence of response

Estimating response rate at 1 year is challenging; some studies have defined response using the Crohn's Disease Activity Index but this is flawed, since it is subjective, poorly-reproducible and non-specific[96]. Further, clinical studies often used adaptive "drop-the-loser" designs[97] after induction, complicating analysis. Accordingly, a HTA-funded systematic review of anti-TNFα therapy was unable to estimate response rates at one year accurately, concluding that "there exists a core of responders of indeterminate size who maintain an anti-TNF dependent response" [7]. Ben-Horin et al reviewed the literature and found loss of response rates varied from 23-46%[13], with most studies close to the upper figure. When added to a 10-20% primary non-response rate from anti-TNFα induction studies [98,99], 50% is an appropriate estimate for the biologic naïve (BN). The prevalence of response at 1 year may be different in those patients previously exposed to anti-TNF-α therapy; a response rate that is 10% lower in those with a past history of anti-TNF-α treatment has been suggested. If such a difference is observed, the proportions of naïve and non-naïve patients would then impact the power of the study for a given sample size. Power calculations assuming a conservative 20% decrease in response rate in the biologic non-naïve and two different combinations of the ratio of naïve to non-naïve patients are presented in the table below. However, we anticipate that most patients recruited will be biologic-naïve, resulting in minimal reduction in power. All subsequent power calculations for secondary outcomes are made assuming 200 patients reach 1-year follow-up, in 100 of whom we expect to observe response/remission.

6.14.1.1.3 Correlation between tests

Moderate (0.5) correlation between tests has been assumed, as both are predicting the same endpoint. Further power calculations assuming lower test correlations have also been conducted to ensure adequate sample size (see 6.14.1.2).

6.14.1.2Calculation

	Ratio of Naïve to	Power	Sensitivity of mMRI	Sensitivity of CRP	Correlation between tests	Prevalence of response / remission	Total N	Total with 30% loss to follow-up

	non-Naive							
A	100:0	0.90	0.60	0.40	0.50	0.50	140	200
B	100:0	0.80	0.60	0.40	0.32	0.50	140	200
C	50:50	0.86	0.60	0.40	0.50	0.45	138	198
D	30:70	0.84	0.60	0.40	0.50	0.43	138	198

A: Total cohort = 200 (200 after 30% loss to follow-up, 100 of whom will have response / remission at one year; 90% power).

6.14.2 Power for secondary outcomes

6.14.2.1 Patients with raised CRP at baseline

As per the assumptions in Section 6.14.1.1.1 above, approximately 60-70% of patients will have raised CRP at baseline. Since we anticipate that 140 patients will reach one year follow-up (after 30% loss to follow-up), 65% corresponds to 91 patients. In this subgroup, CRP normalisation is approximately 60% sensitive for response at 54 weeks (Tables 2 and 4 of reference [21]). The prevalence of response / remission at one year in patients with raised CRP at baseline is approximately 60%, meaning 55 patients will reach this endpoint. Assuming a correlation between tests of 0.4, a sample size of 55 patients with response / remission at one year provides 80% power with alpha=0.05 to detect a 20% greater sensitivity of mMRI improvement vs. CRP normalisation.

6.14.2.2 Prognostic modelling

When developing a prognostic model, the recommended minimum is 10 events per variable (EPV) considered for inclusion in the model[100]. We expect to observe response or remission at one year in 70 patients (i.e. 50% of the 140 patients who will reach one year follow-up). The primary logistic regression model will select from three variables (CRP, mMRI and faecal calprotectin), meaning the number of events per variable will be approximately 23, well in excess of recommended minima.

6.14.2.3 Inter and intraobserver variability

30 measurements by 5 radiologists (inter-observer) and 52 measurements by the same radiologist (intra-observer) permits estimation of intraclass correlation coefficient with 95% confidence interval (CI) width of 0.2 (ref [101] Table 3). Agreement between radiologists for response prediction in our previous work[49] was 0.62; 200 subjects allows calculation of kappa with 95%CI width of 0.3[102].

6.14.2.4 Influence of gut peptides and cytokines on dysmotility

We will compare mean small bowel motility variance (sBmVar) between patients with and without abnormal levels of each gut peptide and cytokine, defining abnormal levels based on the published literature and prior experience. 38 patients permits detection of a 1 standard deviation difference between the two group means with 80% power (beta) at a 5% significance level (alpha), allowing for 30% loss to follow-up. If fewer patients have abnormal levels (e.g. 2:1 ratio), then 44 patients are required; the target sample size is therefore **44 patients.**

6.14.2.5 Body composition and therapeutic response

The primary analysis will use logistic regression to predict response/remission to biologic therapy at one year from the skeletal muscle index. Previous retrospective work has suggested an odds ratio of over 4.0 for primary non-response in the presence of myopenia; if all 140 eligible subjects reaching

one year follow-up (after 30% loss to follow-up) are analysed in this sub-study, study power would be 95% at alpha=5%. If the odds ratio is lower (e.g. 2.7), 140 subjects provides 79% power[103].

6.14.2.6 DW-MRI to predict response

For DW-MRI, the main analysis will use logistic regression to predict response/remission to biologic therapy and will use 4 variables (ADC, Clermont score, CRP and faecal calprotectin). Assuming 10 events per variable (EPV) permits sufficiently stable estimates of regression coefficients, we require 40 events, meaning 80 patients must reach one year follow-up (at prevalence of RoR of 50%, as for the primary outcome). Allowing for 30% loss to follow-up, the target sample size is therefore 88 patients.

6.15 Data Collection, Management and Analysis

6.15.1 Data Collection Methods

Clinical and endoscopic data will be collected onto CRFs by research nurse staff and collaborators who have been trained in CRF completion for this study. CRFs will be provided to recruitment sites by the CCTU and stored locally. Training on CRF completion and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting.

CRP will be measured by local laboratories and use their local QA processes. Calprotectin will be measured by the Royal Devon and Exeter laboratory to minimise variability in absolute measurements between different commercially-available assays [104,105]. In the event of patients not returning their FC samples to Royal Devon and Exeter laboratory for analysis for one or more visit, sites will be contacted to confirm if a clinical result is available. If available this will be collected. Motility MRI will require ROI placement and motility measurement at the central UCL site; these data will then be entered onto a CRF by the relevant radiologist.

CRFs will subsequently be transferred to the UCL CCTU. Data will be entered into the study database by a member of the MOTILITY study team and stored on secure servers based at UCL.

Data collection, data entry and queries raised by a member of the MOTILITY study team will be conducted in line with the CCTU and study specific Data Management plan. Screening logs and enrolment logs will be kept at the study site in a locked cabinet within a secured room. Clinical study team members will receive study protocol training. All data will be handled in accordance with the Data Protection Act 2018.

6.15.2 Non-adherence and non-retention

Outcome data will be collected from all recruited participants who undergo MRI and CRP assessment (i.e. primary comparison) according to the protocol.

CRFs will capture information regarding protocol non-adherence (e.g. completion of PROM questionnaires, stool samples for calprotectin measurement) and a list of Protocol Deviations will be maintained.

Patients who do not complete the baseline and week 12-30 assessments will be replaced if the study is still open for recruitment.

6.15.3 Data Management

Data will be entered in the approved MOTILITY database by a member of the MOTILTIY study team at CCTU, and protected using established CCTU procedures.

Coded data: Participants will be given a unique study Participant Identification Number (PIN). Data will be entered under this identification number onto the central database stored on the servers based at CCTU. The database will be password protected and only accessible to members of the MOTILITY study team at CCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

MRI data (which will also be pseudoanonymised with the relevant PIN) will be stored on Motilent servers, with a copy being held at UCL. Motilent has the following systems in place to ensure confidentiality:

- Motilent will only accept pseudoanonymised data onto its server, requiring several DICOM fields to be masked. These will include (but not limited to) patient name, date of birth, address, NHS number, hospital reference number and examination accession numbers.
- Access is only granted to authenticated named users with a specific username and password, managed by Motilent.
- Secure transfer will be achieved by using Secure Sockets Layer (SSL) protocol via a Hyper Text Transfer Protocol Secure (HTTPS) connection between the user's browser and the Motilent server.
- Data will be encrypted for transfer via the HTTPS/SSL connection using a public key, with the corresponding private key residing only on the Motilent server.
- All results will be returned to the UCL CCTU via encrypted email and using only the PIN.

The database and coding frames have been developed by the Clinical Study Manager in conjunction with CCTU. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the study the database will be retained on the servers of UCL for on-going analysis of secondary outcomes.

The screening and enrolment logs, linking participant identifiable data to the pseudoanonymised Participant Identification Number, will be held locally by the study site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the study the identification, screening and enrolment logs will be stored securely by the sites for at least 10 years unless otherwise advised by CCTU.

6.15.4 Statistical Methods

6.15.4.1 Statistical Analysis Plan

A separate Statistical Analysis Plan will be produced and finalised prior to data lock and transfer to the study statistician. A summary of the methods to be used is provided below.

The analysis will be based on all patients who started treatment and had their visit one scan and CRP, visit two scan and CRP and visit three scan within the timelines defined in the protocol. Participants who become unable to continue with biologic therapy for reasons other than efficacy but have already completed the week 12-30 assessments, they will be deemed to be biologic non-responders and will be analysed as part of the primary outcome population. The primary and secondary outcomes will be based on available cases (i.e. those with sufficient information to assess the study endpoints of response or remission vs. non-response to biological therapy). Analysis for the primary outcome will use logistic regression of diagnostic accuracy measures of MRI and CRP. 95% confidence intervals will be calculated and p-values of <0.05 considered statistically significant.

A similar approach will be used for the secondary outcomes. There will be no adjustment of p-values for secondary outcomes for multiple testing.

6.15.4.2 Statistical Methods – Outcomes

Outcomes are defined in section 6.12.

- **Sensitivity** is defined as the proportion of patients identified with the condition by the index test compared to those identified with the condition by the reference standard.
- **Specificity** is defined as the proportion of patients identified without the condition by the index test compared to those identified without the condition by the reference standard.
- The area under the receiver operating characteristic curve (**AUC ROC**) is obtained from a graph plotting sensitivity against (1-specificity) using the entire range of cutoffs to define a positive result for each index test.

6.15.4.2.1 Primary outcome

Difference in sensitivity between stable or improved MRI-measured segmental small bowel motility *versus* normalisation of C-reactive protein at week 12-30 to predict response or remission (RoR) to biologic therapy at one year.

- Sensitivity for each test (mMRI and CRP) will be reported, with 95% confidence intervals
- McNemar's test will be used for the comparison of paired proportions
- Subgroup analysis will be conducted for: (i) stricturing disease (>50% reduction in luminal calibre) vs. non-stricturing disease, (ii) previous surgery vs. no previous surgery, (iii) therapeutic response defined by non-MRE factors (i.e. clinical failure or pre- and post-treatment endoscopy) vs. MRE-based definition of response, (iv) no previous history of biologic treatment (i.e. biologic naïve) vs. past history of biologic treatment.
- Details for the handling of missing data and sensitivity analyses will be provided in the Statistical Analysis Plan.

6.15.4.2.2 Secondary outcomes

SECONDARY OUTCOME #1

Difference in specificity between stable or improved MRI-measured small bowel motility *versus* normalisation of C-reactive protein at week 12-30 to predict RoR.

- Specificity will be reported for each test, with 95% confidence intervals. McNemar's test will be used to compare the specificities.
- Subgroup analyses will be reported as for the primary outcome.

SECONDARY OUTCOME #2

Difference in area under the receiver operating characteristic curve (ROC AUC) between changes from baseline to the week 12-30 in the continuous small bowel motility MR score and in C-reactive protein levels to predict RoR.

- ROC AUC will be presented for each test, along with the associated 95% confidence interval and the probability value for the comparison between the two curves.
- Subgroup analyses will be the same as for the primary outcome, and will be examined by adding these as interaction terms to the logistic regression models used to calculate ROC AUC.

SECONDARY OUTCOME #3

Difference in prognostic accuracy between changes in the continuous small bowel motility MR score *versus* changes in C-reactive protein levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure (EQ-5D-5L, CUCQ-8 and IBD-Control 8).

- Multivariable regression models will be constructed using the change in the relevant QoL score as the outcome variable, and either change in the MRI-measured small bowel motility or change in CRP between baseline and week 12-30 as continuous explanatory variables.
- Age (continuous), sex (binary), history of previous surgery (binary), presence of perianal disease (binary) and presence of a stoma (binary) will be used as covariates.
- The motility MRI-based model will be compared to the CRP-based model, for each QoL measurement method, to see which test better predicts changes in patient QoL.

SECONDARY OUTCOME #4

Difference in (i) sensitivity and (ii) specificity between stable or improved MRI-measured small bowel motility and normalisation of faecal calprotectin at week 12-30 for predicting RoR. Difference in (iii) ROC AUC between changes from baseline to week 12-30 in small bowel motility and in faecal calprotectin for predicting RoR.

- These analyses will be conducted as for the primary outcome and secondary outcomes #1 and #2, but using faecal calprotectin as the comparator to MRI-measured small bowel motility (rather than CRP).

SECONDARY OUTCOME #5

Difference in prognostic accuracy between changes in the continuous MRI-measured small bowel motility score *versus* changes in faecal calprotectin levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure.

- This analysis will be conducted as for secondary outcome #3, but using faecal calprotectin as the comparator to MRI-measured small bowel motility (rather than CRP).

SECONDARY OUTCOME #6

Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including MRI-measured small bowel motility *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.

- Prognostic models based on binary logistic regression using RoR at one year (defined as for the primary outcome) as the outcome variable and either change from baseline to week 12-30 in MRI-measured small bowel motility, CRP or faecal calprotectin as the main predictor variables.
- Subgroup analyses will be the same as for the primary outcome, and will be examined by adding these as interaction terms to the logistic regression model.
- Additional predictor covariates of non-response to biological therapy will be finalized once data from the Personalised Anti-TNF therapy in Crohn's disease (PANTS) study are available, but are likely to include age at diagnosis (continuous), Montreal subtype of disease (categorical), current use of tobacco (binary), presence of perianal disease (binary). All predictor covariates will be prespecified based on evidence from the literature and PANTS, thereby conserving statistical power for the comparison between MRI, CRP and faecal calprotectin rather than for variable selection.

- The full details of model selection and specification, approach to missing data, methods for assumption checking, internal validation, and assessment of model performance will be specified in the full Statistical Analysis Plan. This will adhere to the principles of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement[106].

SECONDARY OUTCOME #7

Interobserver variability of MRI-measured small bowel motility for (a) experts in mMRI and (b) experienced radiologists without prior mMRI experience. Intraobserver variability of MRI-measured small bowel motility for experts in mMRI.

- Small bowel motility will be quantified by a minimum of 2 expert readers (all scans); with a subset of 30 scans being interpreted by 5 experienced radiologists who are unfamiliar with MRI motility quantitation (inter-observer variability, for both experts and experienced radiologists).
- 52 scans will be re-measured by the same expert reader after a 3 month wash-out period (intra-observer variability).
- Agreement for the magnitude of small bowel motility will be quantified using the intra-class correlation coefficient (ICC).
- As discussed in section 6.7.1, it is possible for numerical agreement between two readers' absolute values of MRI-measured small bowel motility to be relatively small, but the overall agreement in terms of the test result (i.e. prediction of response/remission vs. non-response) to be good. The latter (i.e. treating each pair of motility MRI measurements as an individual test result, either positive or negative) will be quantified using unweighted kappa.

SECONDARY OUTCOME #8

Difference in (a) plasma levels of (i) gut peptides and (ii) inflammatory cytokines and (b) small bowel motility variance between patients with and without RoR.

- Mean levels of each gut peptide (GLP-1 and PYY) and cytokine (IL-1, IL-6, IL-10) will be compared between the two groups; the precise statistical test to be used will depend on the distribution characteristics of the observed data.
- Mean small bowel motility variance will be compared between the two groups with an appropriate statistical test for the distribution of the observed data.
- The mean (or other measure of central tendency if appropriate) and standard deviation (or other appropriate measure of dispersion) will be reported for each group, and a probability value for the comparison between the two groups.

SECONDARY OUTCOME #9

Difference in small bowel motility variance between patients with normal and elevated levels of (a) gut peptides (b) inflammatory cytokines and (c) between patients with and without abdominal symptoms at each time point.

- Abnormal levels of gut peptides (GLP-1 and PYY) and cytokines (IL-1, IL-6 and IL-10) will be defined using the published literature and prior data (for example, using >200pg/ml for PYY[81]).
- Mean small bowel motility variance (SBmVar) will be defined as the variance of the Jacobian determinant value within a radiologist-drawn ROI that encompasses the whole of the small bowel.
- SBmVar will be compared between the two groups of patients with normal vs. abnormal peptide / cytokine levels using an appropriate statistical test for the distribution of the observed data.

- Symptoms of diarrhoea and abdominal pain will be quantified using the relevant CUCQ-8 items; general wellbeing will be quantified using the EQ-5D-5L.
- The mean (or other measure of central tendency if appropriate) and standard deviation (or other appropriate measure of dispersion) will be reported for each group, and a probability value for the comparison between the two groups.
- An exploratory analysis will fit regression models to predict patient symptom scores from SBmVar, gut peptides and inflammatory cytokines, using data from all time points, and robust estimates of the standard errors to take account of the mixture of between and within patient information. Explanatory variables may be categorised as normal or raised, depending on the distribution of each variable.

SECONDARY OUTCOME #10

Difference in response rates to biological therapy at one year for (a) patients with and without skeletal muscle myopenia and (b) patients with and without low skeletal muscle:fat ratios.

- Binary logistic regression will be used to compare between the two groups, with RoR as the outcome and myopenia skeletal muscle index as the main explanatory variable.
- A pre-specified sensitivity analysis will use low skeletal muscle:fat ratio as the explanatory variable rather than low skeletal muscle index.
- Other covariates associated with non-response to biological therapy will be chosen as for secondary outcome #6, and again will be pre-specified using PANTS data and the published literature.
- An odds ratio for each variable included in the final model will be provided, with associated 95% confidence intervals.
- An exploratory analysis will use regression models to predict skeletal muscle index or skeletal muscle:fat ratio.
- An exploratory analysis will examine the association between body composition and therapeutic drug trough levels (where these are available).

SECONDARY OUTCOME #11

Sensitivity and specificity of (a) >10% increase in ADC and (b) >25% reduction in Clermont score between weeks 0 and 12-30 for RoR to biologic therapy at one year.

- Sensitivity and specificity will be reported for each parameter, with 95% confidence intervals. McNemar's test will be used to compare sensitivity and specificity between ADC alone and the full Clermont score.
- Subgroup analyses will be as for the primary outcome.

SECONDARY OUTCOME #12

Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including change in ADC value derived from DW-MRI between baseline and week 12-30 *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.

- Prognostic models based on binary logistic regression using RoR at one year (defined as for the primary outcome) as the outcome variable and either change from baseline to week 12-30 in ADC value, CRP or faecal calprotectin as the main predictor variables.
- Subgroup analyses will be the same as for the primary outcome, and will be examined by adding these as interaction terms to the logistic regression model.

- Additional predictor covariates of non-response to biological therapy to be finalised after PANTS data are available.
- As for secondary outcome #6, the full details of model selection and specification, approach to missing data, methods for assumption checking, internal validation, and assessment of model performance will be specified in the full Statistical Analysis Plan. This will adhere to the principles of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement

SECONDARY OUTCOME #13

Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models including the Clermont score derived from DW-MRI *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.

- Prognostic models based on binary logistic regression using RoR at one year (defined as for the primary outcome) as the outcome variable and either change from baseline to week 12-30 in Clermont score, CRP or faecal calprotectin as the main predictor variables.
- This analysis will be conducted as for secondary outcome #11, but using change in Clermont score as the predictor variable, rather than change in ADC.

SECONDARY OUTCOME #14

Difference in prognostic accuracy between changes in the Clermont score *versus* changes in (i) C-reactive protein and (ii) faecal calprotectin levels at week 12-30 to predict clinically significant improvements from baseline to one year in each quality of life measure.

- Multivariable regression models will be constructed as for secondary outcome #3, but using the Clermont score instead of the MRI-measured small bowel motility.
- Covariates will be as for secondary outcome #3.

SECONDARY OUTCOME #15

Incremental prognostic value of DW-MRI parameters in conjunction with motility MRI scores for response to biologic therapy at one year.

- Prognostic models based on binary logistic regression using RoR at one year (defined as for the primary outcome) as the outcome variable.
- The prognostic accuracy of a model using MRI-measured small bowel motility (in conjunction with PANTS-derived predictor covariates) will be compared with that of a more complex model that includes both MRI-measured small bowel motility and the Clermont score derived from DW-MRI.

SECONDARY OUTCOME #16

Difference in prognostic accuracy and incremental prognostic value of multivariate prognostic models between baseline and week 12-30 *versus* those including (i) C-reactive protein and (ii) faecal calprotectin for response to biologic therapy at one year.

- Prognostic models based on binary logistic regression using RoR at one year (defined as for the primary outcome) as the outcome variable and either change from baseline to week 12-30 in CRP or faecal calprotectin as the main predictor variables.
- Subgroup analyses will be the same as for the primary outcome, and will be examined by adding these as interaction terms to the logistic regression model.

- Additional predictor covariates of non-response to biological therapy to be finalised after PANTS data are available.

SECONDARY OUTCOME #17

Difference in prognostic accuracy between multivariate prognostic models between baseline and week 12-30 *versus* those including (i) motility MRI alone, (ii) DW-MRI alone, and (iii) combined motility+DW-MRI features for response to biologic therapy at one year.

- Prognostic models based on binary logistic regression using RoR at one year (defined as for the primary outcome) as the outcome variable.
- All models will use pre-specified clinical predictor covariates derived from PANTS.

7. Oversight and Study Committees

Study oversight is intended to preserve the integrity of the study by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, adherence to study follow up and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent study oversight complies with the UCL CCTU trial oversight policy.

In multi-centre studies such as MOTILITY, this oversight is considered and described both overall and for each recruiting centre by exploring the study dataset or performing site visits as described in the MOTILITY study Quality Management and Monitoring Plan.

7.1 Study Committees

7.1.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the study. The group will comprise the co-Chief Investigators, principal investigators for participating sites and other lead investigators (clinical and non-clinical) and members of the UCL CCTU, as well as a patient representative. The TMG will be responsible for the day-to-day running and management of the study. It will meet at least once a year. Further details are available in the TMG Terms of Reference (ToR).

7.1.2 Joint Trial Steering Committee and Data Monitoring Committee (TSC/DMC)

The Joint Trial Steering Committee and Data Monitoring Committee (TSC/DMC) is the independent group responsible for oversight of the study in order to safeguard the interests of study participants. As they are a joint DMC they will also be responsible for safeguarding the interests of study participants, monitoring the accumulating data. The TSC/IDMC will provide advice to the Chief Investigators, UCL CCTU, the funder (EME) and sponsor on all aspects of the study through its independent Chair.

Further details of the roles and responsibilities of the Committee, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the MOTILITY Terms of Reference (ToR).

7.1.3 Study Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the study. UCL is the study sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

7.2 Safety reporting

Adverse reactions are not expected within this study as the interventions are minimal, used in routine care and well-established, with a highly-developed safety profile. All adverse events will be recorded in the patient notes as per standard care. Due to the nature of Crohn's Disease, this patient population will experience disease symptoms and disease exacerbation unrelated to imaging throughout the duration of the study. Although we do not require MRI to be performed with the intravenous contrast agent, gadolinium, as part of the minimum imaging dataset, some sites may choose to administer it on occasion or as routine. Therefore, there may be adverse reactions to this agent. Such reactions are well established within the profile, and gadolinium contrast is not an Investigational Medicinal Product (IMP). Similarly, patients in this study will (by definition, to meet the inclusion criteria) be receiving biologic therapy as part of their routine clinical care. The agents will not be administered as IMPs, have a well-established safety profile, and therefore will not be routinely reported.

All Serious Adverse Events (SAEs) will be recorded in the patient notes as per standard practice, if any SAEs become suspected unexpected serious adverse reactions (SUSARs)as assessed by the Principal investigator at the site and are related to the research MRI which the patients will need to undergo as part of the MOTILITY trial, these will be reported to the sponsor within the relevant timeframes.

The sponsor will be responsible for forwarding the SUSAR to the independent clinician as well as to REC and other participating sites. Should the sponsor have any queries, these will need to be addressed by the reporting site promptly.

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this study.

7.2.1 Guidance of Adverse Event Inclusions and Exclusions specific to this study

Adverse events or reactions to be reported to the UCL CCTU:

- Those which fulfil the definitions of a SUSAR and are related to research MRI

Adverse events or reactions NOT to be reported:

- Those which are related directly to the study interventions (i.e. MRI, CRP and faecal calprotectin performed according to the study protocol).
- Any changes in or complications related to a participant's underlying Crohn's disease (including its further assessment or treatment, including planned ileocolonoscopic assessment or surgery) not related to the study interventions.

Seriousness and causality will be judged by the relevant site investigator responsible for the care of the participant (see 7.2.4.1 and 7.2.4.2 below).

7.2.2 Other notifiable events

The following incidental findings should be reported to the sponsor within relevant timelines:

- Abscess requiring urgent drainage
- Deep vein thrombosis
- Malignancy
- Bowel Obstruction
- Perforation
- Any other important incidental findings, in the opinion of the site radiologist reviewing the mMRI scan

7.2.3 Procedure to follow in the event of participants becoming pregnant

MRI is relatively contraindicated in pregnancy and so pregnancy is an exclusion criterion for this study; eligible patients who are recruited will undergo assessment for possible pregnancy (including pregnancy testing where appropriate) as per normal clinical practice at that recruitment site prior to their MRI scan. Participants who become pregnant during the course of the study will be treated as per usual care; but will be excluded from the study as they will be unable to undergo study assessments to inform the primary outcome. A replacement participant will be recruited to preserve sample size, as long as the study is still open to recruitment.

7.2.4 Investigator responsibilities relating to safety reporting to UCL CCTU

All serious adverse events (SAEs) and serious adverse reaction (SARs) should be recorded in the patient's medical notes. All SUSARs relate to research MRI should be documented in the patient notes and notified to the UCL CCTU within 24 hours of the investigator becoming aware of the event.

7.2.4.1 Seriousness assessment

Seriousness will be arbitrated by the investigator responsible for the care of the participant, using the definitions given in the table below.

Description of the event	Notes
Results in death	
Is life-threatening	i.e. the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a non-severe myocardial infarction)
Requires hospitalisation or prolongs existing hospitalisation	Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute a serious event.
Results in persistent or significant disability or incapacity	
Is a congenital anomaly or birth defect	
Is another important medical condition	Medical judgement should be exercised. This may include events that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

7.2.4.2 Causality assessment

The investigator must assess the causality of all serious events or reactions in relation to the study interventions using the definitions provided in table below

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after the intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the scan). However,

	the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The cells above require documentation in the patient notes if the event or reaction is deemed serious as per Table 1; however, they do not require notification to the UCL CCTU unless they are related to research MRI (see 7.2.4.3 below)

7.2.4.3 Expectedness

If there is at least a possible involvement of the study interventions, the investigator and sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported as a recognised reaction to study interventions (including the oral and/or intravenous contrast media administered for MRI scanning), or one that is more frequently reported or more severe than previously reported. Individual sites should retain a copy of the Summary of Product Characteristics (SPC) for their chosen oral contrast media used for MRI (and, if used, for the chosen intravenous contrast agent). If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and REC reporting guidelines apply (see Notifications sections of the protocol).

7.2.5 Notifications

7.2.5.1 Notifications by the Investigator to CCTU

The UCL CCTU must be notified of all SUSARs which are deemed related to the research MRI, immediately of the investigator becoming aware of the event, and must be notified to the UCL CCTU until study closure.

The incidental findings and serious adverse events related to mMRI form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with confirmation of the grading (i.e. seriousness), causality and expectedness of the event. In the absence of the responsible investigator, the SUSAR form should be completed and signed by a member of the site study team and emailed as appropriate within the timeline. The responsible investigator should check the SUSAR form at the earliest opportunity, make any changes necessary, sign and then email to CCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SUSAR are the study number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness, causality and expectedness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available in follow up reports.

The SUSAR form must be scanned and sent by email to the study team at the UCL CCTU on **ctu.motility@ucl.ac.uk**

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or study follow-up if necessary. Follow-up forms (clearly marked as follow-up) should be completed and emailed to CCTU as further information becomes available. Anonymised additional information and/or copies of test results etc may be provided separately. The participant must be identified by study number, date of birth and initials only. The

participant's name should not be used on any correspondence and should be blacked out and replaced with study identifiers on any test results.

7.2.5.2 UCL CCTU responsibilities

Medically qualified staff at the UCL CCTU and/or the Chief Investigators (CI or a medically qualified delegate) will review all safety reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

All safety reports will also be reviewed by an Independent Safety Clinician, who will report to the joint DM / TSC.

The delegated staff at the UCL CCTU will review the assessment of seriousness, expectedness and causality, and, based on possible wider knowledge of the reference material for the interventions, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

The UCL CCTU is undertaking the duties of study sponsor and is responsible for the reporting of SUSARs to the REC. Fatal and life threatening SUSARs must be reported to the REC within seven days of the UCL CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

The UCL CCTU will keep investigators informed of any safety issues that arise during the course of the study.

7.3 Quality Assurance and Control

7.3.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the MOTILITY study are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the study and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including study design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the study is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the study related activities are fulfilled.

7.3.2 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The study database will also be programmed to generate reports on errors and error rates. Essential study issues, events and outputs, including defined key data points, will be detailed in the MOTILITY study Data Management Plan.

7.3.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the MOTILITY Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports.

7.3.4 Direct access to participant records

Participating investigators must agree to allow study related monitoring, including audits, REC review and other inspections, by providing access to source data and other study related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the study.

8 Ethics and Dissemination

8.1 Research Ethics Approval

Before initiation of the study at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the study at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) NHS permissions and approval.

The rights of the participant to refuse to participate in the study without giving a reason must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After recruitment the participant must remain within the study for the purpose of follow up and data analysis. However, the participant remains free to change their mind at any time about the study follow-up without giving a reason and without prejudicing their further treatment.

8.2 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

8.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are recruited to the study.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the UCL CCTU Protocol Review Committee.

8.4 Protocol Amendments

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be submitted to the REC by the UCL CCTU and distributed by the Study Management Team to relevant parties (e.g. investigators, REC, study participants, study registries, journals and regulators). The decision to amend the protocol will be at the discretion of the TMG.

8.5 Consent

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the study, at any time and for any reason, without incurring any penalty or affecting their treatment.

As this study is not a clinical trial of an investigational medicinal product, 16 and 17 year old patients will be consented as adults.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the participant information sheet and the participant will be asked to sign an updated consent form. These will be approved by the Research Ethics Committee prior to their use. A copy of the approved consent form is available from the UCL CCTU Study Team.

Patients will also be asked to consent to use of their anonymised data (both imaging and clinical) and for their anonymised imaging and clinical data to be stored and used for future related research. Independent of this, participants will be asked to consent to the study team accessing their routine clinical follow-up data for a period of 5 years after treatment initiation, to determine their longer-term outcome. This will be independent of their consent to the main study (1 year follow-up).

Patients may withhold or withdraw consent for the study and/or data use for future research without affecting their participation in the main study if agreed.

8.5.1 Consent in Ancillary Studies

Patients will consent to take part in the gut peptide / inflammatory cytokine sub-study and/or Diffusion Weighted MRI sub-study, independent from consent to the main study. Separate consent will not be sought for either the inter/intra-observer variability or the body composition sub-studies, as these do not require any additional data collection or participant procedures.

8.6 Confidentiality

The EU General Data Protection Regulation (GDPR) and UK Data Protection Act 2018 will be followed in this study.

Patient identifiable data will be kept at the hospital site and no data will be received at the UCL CCTU unless it is pseudoanonymised. Any personal data sent to the lead team at UCLH will use secure communication approved for such purposes by NHS data protection emails (e.g. secure NHS email such as NHS.net or NHSmail 2 once transition is complete). UCL CCTU will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner. The study will be registered in accordance with the Data Protection Act 2018 with the Data Protection Officer at UCL.

8.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the study. Stuart Taylor undertakes paid research consultancy for Robarts Clinical Trials. Andrew Plumb has provided paid educational lectures for Actavis, Acelity and Janssen.

8.8 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical study. UCL 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 not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigators, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

8.9 Finance

The main MOTILITY study is funded by the Efficacy and Mechanism Evaluation Programme following a commissioned call; EME reference number 14/201/16. The diffusion-weighted MRI sub-study is funded by the NIHR Fellowships programme. It is not expected that any further external funding will be sought.

8.10 Archiving

The investigators agree to archive and/or arrange for secure storage of MOTILITY study materials and records for a minimum of 5 years after the close of the study unless otherwise advised by the CCTU.

8.11 Access to Data

Requests for access to study data will be considered, and approved in writing where appropriate, after formal application to the TMG. Considerations for approving access are documented in the TMG Terms of Reference. As stipulated by the NIHR, raw (anonymised) imaging data will be made publicly available after study closure and analysis according to the MOTILITY study data access plan.

8.12 Publication Policy

8.12.1 Study Results

Data will be presented at national and international conferences and published in peer-reviewed journals. Our patient representatives will ensure dissemination to patient groups via Crohn's and Colitis UK. A full report of the main study will be provided to the National Institute for Health Research, Efficacy and Mechanism Evaluation programme, and published in their journal. The results of the diffusion –weighted MRI sub-studywill be reported separately to the NIHR Fellowship programme. Data will be pseudonymous during the study; only fully anonymised data will be published, without any identifiers. Patients will be informed of the study results during outpatient follow-up appointments. The results of the study will be disseminated regardless of the ultimate findings.

8.12.2 Authorship

The TMG will oversee the publication and presentation of the data to peer reviewed journals and scientific meetings. All members of the TMG will approve publications. The writing committee will be led by the co-Chief Investigators and include TMG members. All site PIs and lead radiologists will be invited to join the MOTILITY Study Investigators group, and will be acknowledged as authors of the study report of the primary outcome, the report to the funder, and other study-related publications as appropriate (subject to approval by the TMG).

8.13.3 Reproducible Research

The study protocol will be published and made publicly available early in the study. Datasets will be made available after study closure and an embargo period, as stipulated in the MOTILITY study data access plan.

9 Protocol Amendments

This is version 6.0. This protocol has been amended as follows:

Protocol version	Major changes from prior version	REC substantial amendment?
6.0	The number of participants that can be recruited has been increased to account for the high attrition rate observed and to ensure we can reach our planned target sample size, which remains unchanged. Visit 3 mMRI scan timeline has been extended from one year (+/- 8 weeks) to one year (-8 weeks / + 26 weeks) Ultrasound sub-study has been discontinued as funding is no longer available Consent timelines have been extended provided motility sequences are done as part of standard care within study timelines CRP requirement at visit 3 is no longer an absolute requirement Standard of care clinical Faecal Calprotectin results will be collected in the event a patient does not return their sample to the central laboratory for analysis	Yes
5.0	The sample size has been increased to account for the higher than anticipated rate of patient attrition. Inclusion criteria expanded to allow for patients starting treatment prior to informed consent to be eligible Inclusion criteria expanded to allow for patient's eligibility to be confirmed within 90 days prior to treatment start or within 14 days after first treatment dose. Visit 2 timelines have been increased to 12 – 30 weeks Faecal Calprotectin sample collection timelines increased to within 14 days after first treatment dose	Yes
4.0	CRP collection at baseline to be within 3 months prior to start of treatment and 2 days post treatment	Yes
3.0	- Inclusion of patients being treated with a range of biological therapies, including anti-interleukins - Addition of DW-MRI sub-study - Addition of SBUS sub-study	Yes
2.0	- Clarification of eligibility criteria - Inclusion of patients with prior biological treatment(s) - Permission of active small bowel disease to be confirmed by modalities other than colonoscopy and MRI - Refinement of subgroup analysis for the primary outcome to include all patients with non-MRE-based definitions of response (rather than just those with endoscopically defined response).	Yes
1.0	n/a, this was the original REC-approved protocol	n/a

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