National Institute for Health Research

UCL Comprehensive Clinical Trials Unit

Short title:

METRIC-EF (**M**agnetic resonance **E**nterography (MRE) or ul**TR**asound **I**n **C**rohn's disease **E**xtended **F**ollow-up for predicting disabling disease)

Full Title

METRIC-EF: Magnetic Resonance Enterography and Small Bowel Ultrasound as predictors of disabling disease in newly diagnosed Crohn's disease

Version	4.0
Date	10May2022
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2015/198
Trial registration	ISRCTN76899103
REC #	18/LO/1930

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 5. It describes the METRIC-EF study, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial'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 trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its trials 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 trial 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) UK Policy Framework for Health and Social Care. 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 trial, or
- The scientific value of the trial.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the METRIC-EF trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director or via the Trial Team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN76899103	
Date of Registration in Primary Registry	12Mar2019	
Secondary Identifying Numbers	CTU/2015/198	
Source of Monetary or Material Support	National Institute for Health Research (NIHR) Health Technology Assessment (HTA 15/59/17) and Fellowships Programmes (PDF-2017-10-081)	
Sponsor	University College London with sponsor responsibilities delegated to CCTU	
Contact for Public Queries	ctu.enquiries@ucl.ac.uk	
Contact for Scientific Queries	Prof Stuart Taylor Professor of Medical Imaging Centre for Medical Imaging 3rd Floor East 250 Euston Rd London NW1 2PG stuart.taylor1@nhs.net 020 3549 5659 (PA)	Dr Andrew Plumb Associate Professor of Medical Imaging Centre for Medical Imaging 3rd Floor East 250 Euston Rd London NW1 2PG andrew.plumb@nhs.net 020 3549 5659 (PA)
Public Title	METRIC-EF (Magnetic resonance Enterography (MRE) or ulTRasound In Crohn's disease Extended Follow-up for predicting disabling disease	
Scientific Title	METRIC-EF: Magnetic Resonance Enterography (MRE) and Small Bowel Ultrasound (SBUS) as predictors of disabling disease in newly-diagnosed Crohn's disease	
Countries of Recruitment	England and Scotland	
Health Condition(s) or Problem(s) Studied	Crohn's disease	
Intervention(s)	This study involves extended follow-up of a previously-recruited cohort of individuals recruited on the recently concluded METRIC trial and new patients with recent diagnosis of Crohn's disease; there are no further direct patient interventions as part of the current study. Participants will have already undergone: • Magnetic Resonance Enterography (MRE), 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, which can then be evaluated for signs of Crohn's disease (as well as other conditions). The severity of the condition can be measured and quantified using validated scoring systems.	

	• Blood, stool and endoscopic tests as part of their routine clinical care The present study aims to determine if abnormalities in MRE at diagnosis can predict which patients are destined to develop severe ("disabling") Crohn's disease, defined using existing definitions from the literature
Key Inclusion and Exclusion Criteria	**Participant Inclusion Criteria:** METRIC cohort • Enrolled in the METRIC study, new diagnosis cohort AND • Formed part of the final new diagnosis cohort (i.e. with a confirmed diagnosis of Crohn's disease and underwent relevant study interventions and follow-up). METRIC new diagnosis cohort inclusion criteria were: o Aged 16yrs or more o Newly diagnosed with Crohn's disease based on endoscopic, histological, clinical and radiological findings, OR o Highly suspected of Crohn's disease based on characteristic endoscopic, imaging and/or histological features but pending final diagnosis (only participants who ultimately were confirmed to have Crohn's disease will continue in this extension study) AND o Have given signed consent to be part of METRIC-EF **Participant Exclusion Criteria:** METRIC cohort • Enrolled in the METRIC study but not part of the final new diagnosis cohort **Participant Inclusion Criteria:** Retrospective cohort • Aged 16yrs or more and received a new diagnosis of Crohn's disease based on endoscopic, histological, clinical and radiological findings • Dedicated enteric imaging (MRE) acquired according to the standards of the METRIC study and performed either <3months after, or <3months prior to the new diagnosis of Crohn's disease • Institutional practice is to perform MRE in all participants with newly diagnosed Crohn's disease • Has >4yrs clinical follow-up data, or anticipated to have such follow-up data by the time of consensus endpoint meetings (mid 2021), at recruiting hospital
Study Type	Extended follow-up of a non-randomised, prospective, multicentre cohort study.
Date of First Enrolment	April 2019
Target Sample Size	207
Primary Outcome(s)	Comparative predictive ability of prognostic models incorporating MRI severity scores (MEGS, sMaRIA and Lémann index) to improve predictions from a model based on clinical characteristics alone to predict the development of disabling disease at 5 year follow-up.
Key Secondary Outcomes	1. Comparative predictive ability of prognostic models incorporating MRI severity scores (MEGS, sMaRIA, Lémann index) to improve predictions

	from a model based on clinical characteristics alone to predict the development of Montreal B2 / B3 disease or Liège severe disease at 5 year follow-up. 2. Identification of the best combination of individual MRE features for prediction of disabling Crohn's disease (all definitions) within 5 years of new diagnosis. 3. Average per-patient and national healthcare costs incurred within 5 years of a new diagnosis of Crohn's disease. 4. Patient, disease phenotype and imaging characteristics associated with higher economic costs within 5 years of diagnosis.

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF 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
Dr Susan Mallett	University of Birmingham	Study Statistician
Dr Marta Campos	UCL CCTU	Clinical project manager
Sue Philpott	UCL CCTU	Study manager
Grace Auld	UCL CCTU	Clinical project manager

1.4.2 Role of trial 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.
Health Technology Assessment Programme	NIHR	Funder; no influence over data collection, interpretation or decision to submit for publication

1.4.3 Trial Team

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

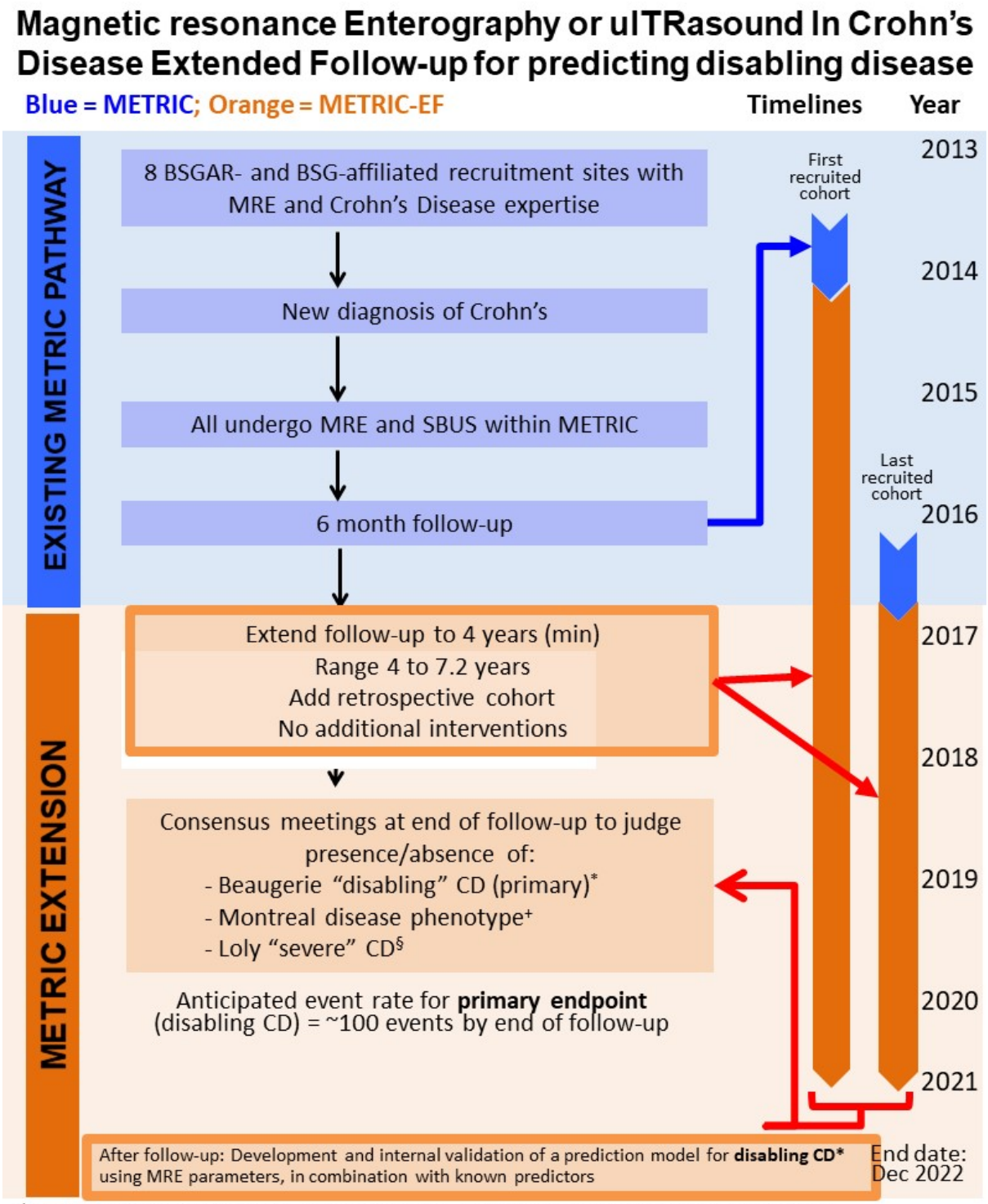
1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Stuart Taylor	UCL Medicine	Co-Chief Investigator & Radiologist
Dr Andrew Plumb	UCL Medicine	Co-Chief Investigator & Radiologist
Dr Stuart Bloom	UCLH	Gastroenterologist
Professor Simon Travis	Oxford	Gastroenterologist
Dr Ailsa Hart	St Mark's	Gastroenterologist
Dr John Hamlin	Leeds	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
Dr Susan Mallett	University of Birmingham	Statistician
Kashfia Chowdhury	UCL CCTU	Statistical Oversight
Grace Auld	UCL CCTU	Clinical project manager
Sue Philpott	UCL CCTU	Study manager

1.4.5 Joint Data Monitoring and Trial Steering Committee

Name	Affiliation	Role and responsibilities
Vicky Goh	Kings College	Radiologist
James Lindsay	Barts, London	Gastroenterologist
Andrea Marshall	Warwick	Independent Statistician
Ilan Jacobs	Citigroup	Public Representative

2 Trial Diagram



*Any of: 2+ steroid courses, hospitalization, surgery or >12m of severe symptoms
+B1 = inflammatory, B2 = stricturing, B3 = penetrating
§Any of: complex perianal CD, colonic resection, 2+ small bowel resections, definitive stoma

METRIC=magnetic resonance enterography or ultrasound in Crohn's disease; CD = Crohn's disease; MRE = magnetic resonance enterography;BSGAR = British Society of Gastrointestinal and Abdominal Radiology; BSG = British Society of Gastroenterology

3 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

CD	Crohn's Disease
CI	Chief Investigator
CRF	Case Report Form
CRP	C-Reactive Protein
CCTU	Comprehensive Clinical Trials Unit
EC	Ethics Committee
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
HBI	Harvey Bradshaw Index
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFX	Infliximab
IRB	Institutional Review Board
ITT	Intention to Treat
LI	Lemann Index
mAbs	Monoclonal antibodies
MaRIA	Magnetic Resonance Index of Activity
MEGS	Magnetic Resonance Enterography Global Score
MRE	Magnetic Resonance Enterography
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic
SB	Small Bowel
SBUS	Small Bowel Ultrasound
SES-CD	Simple Endoscopic Score for Crohn's Disease
SLIC	Sonographic Lesion Index for Crohn's Disease
s-MARIA	Simple Magnetic Resonance Index of Activity
Sn	Sensitivity
Sp	Specificity
SSA	Site Specific Approval
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TNFα	Tumour Necrosis Factor Alpha
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospital
USAI	Ultrasound Activity Index

4 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.

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 participants. 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.

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.

Lemann Index (LI) uses MRI (vide infra) to quantify the total amount of bowel damage sustained due to Crohn's disease.

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.

Magnetic Resonance Index of Activity (MaRIA) is a validated semi-quantitative scoring system that estimates the degree of inflammation in the bowel as measured by MRI. See also sMaRIA.

Magnetic Resonance Enterography Global Score (MEGS) is a different validated semi-quantitative scoring system that also estimates the degree of inflammation in the bowel at MRI

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.

Pseudonymised (***with respect to Retrospective cohort***) – data received at CCTU is anonymised but link for data linkage remains at site.

sMaRIA is a simplified version of the MaRIA which is easier to calculate but equally reliable.

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.

5 Introduction

5.1 Background and Rationale

Crohn's disease (CD) is a chronic, relapsing and remitting inflammatory disease of the gastrointestinal (GI) tract affecting approximately 80,000 people in the UK[1]. The small bowel (SB) and colon are most commonly affected, and clinical manifestations range from subtle bowel surface ulceration through to advanced disease, which may be complicated by stricturing, fistulas and abscesses. Most patients are younger than 25 years when the diagnosis is made, meaning that CD can cause decades of ill health and poor quality of life (QoL). 30% of patients with CD need regular hospital care[2], and 50-80% need surgery[1]. 25% and 15% of patients cannot work fully at 1 and 10 years respectively[3], adding financial distress to their physical burden[4]. Lifetime treatment costs are £15k-£120k/patient, similar to heart disease, and a major financial challenge to the NHS.

There is no single test for CD; diagnosis depends on a combination of clinical, endoscopic, biochemical, histopathological and radiological factors. Imaging is crucial because the SB is relatively difficult to assess via conventional endoscopic means; approximately 40% of patients will have SB disease beyond the reach of an endoscope[5]. Accordingly, pan-European consensus recommends that patients with suspected CD undergo SB imaging as well as endoscopy at diagnosis[6]. Historically, imaging has primarily provided diagnostic information concerning the presence or absence of CD. More recently, imaging is increasingly used to objectively quantify CD anatomical distribution, severity, biological activity and treatment response. Accordingly, clinical practice has moved away from conventional fluoroscopic imaging (using barium suspension to make the bowel visible to X-rays) to cross-sectional techniques, notably MR enterography (MRE) and small bowel ultrasound (SBUS). MRE and US are complementary to endoscopy, and both are increasingly validated to stage and monitor CD, thereby helping to guide therapeutic decision-making[7-10]. The success of MRE and US as staging and monitoring tools raises the intriguing possibility that they could also be used help predict patient outcome. Since imaging features reflect disease pathophysiology[7,11,12], these same features may be able to accurately triage CD into alternate imaging phenotypes with correspondingly different prognoses, thereby facilitating individualised treatment.

5.1.1 CD treatment strategies

Traditionally, CD treatment aimed to improve symptoms and QoL. Indeed, some patients with mild disease may not need medical intervention and 25-50% never require immunomodulatory drugs. However, for most patients this is inadequate because uncontrolled active inflammation in CD causes progressive bowel damage, ultimately leading to hospitalization, surgical resection or even death. Waiting until symptoms or signs of active CD develop, and then treating at that stage (so-called "bottom-up therapy") is insufficient, because CD can be active (and causing bowel damage) even when the patient feels relatively well[13]. Indeed, by the time symptoms are severe enough to precipitate treatment, irreversible bowel injury may have already occurred. The alternative strategy is to institute early, aggressive treatment and suppress inflammation before such damage has a chance to accumulate – "top-down therapy". This approach focuses on prevention of complications rather than simply reacting to symptoms, thereby reducing adverse consequences such as surgery and hospitalization.

Monoclonal antibodies directed against the tumour necrosis factor alpha cytokine (anti-TNFα mAbs) are the crucial agents in the top-down paradigm, whether used alone or in combination with other immunomodulators such as azathioprine (AZA) or methotrexate (MTX). These agents (such as

infliximab (IFX) and adalimumab (ADA), as well as their newly available biosimilar analogues[14]) are extremely effective at improving symptoms and healing the bowel. Indeed, full mucosal (or transmural) healing is now the aim in CD treatment[15]. However, anti-TNFα mAbs are inconvenient to administer (needing injection or infusion), have side-effects in >10%[16] (e.g. infection–occasionally life-threatening[17]) and may increase cancer risk. They are also expensive (c.£10k / patient / annum), accounting for 2/3 of CD healthcare costs[18]. This raises a dilemma; anti-TNFα agents are effective for many[19], but their costs and side-effects mean they cannot and should not be administered to all – targeting is needed. Such targeting implies an urgent need for robust methods to identify patients who are most likely to benefit from top-down therapy – i.e. predicting those individuals destined to develop severe CD. This proposal aims to use imaging, specifically MRE, to help address this problem, and answer the question: "Do MRE features at diagnosis improve prediction of disabling Crohn's disease within 5 years of diagnosis?"

5.1.2 The METRIC study

METRIC (Magnetic Resonance Enterography or Ultrasound In Crohn's Disease) study (ISRCTN03982913), HTA 11/23/01, was a multicentre, prospective imaging trial performed in 8 NHS centres that was designed to compare the diagnostic accuracy of MRE and US for the location and extent of CD[20]. Consenting adult patients presenting with either a new diagnosis of CD, or presenting with an acute symptomatic exacerbation ("flare") of known CD, were recruited and all underwent both MRE and US examinations. These were performed by radiologists, representative of UK practice, who were blinded to other clinical information. Patients were followed up for a minimum of 6 months, at which point a consensus panel used all available information (including clinical, biochemical, imaging, endoscopic, surgical, and histopathologic data) to determine the location and extent of each individual patient's CD, thereby providing a robust reference standard against which to judge the diagnostic accuracy of MRE and US[21]. Although METRIC was conceived as a comparative diagnostic accuracy study, it affords the opportunity to determine if imaging features at diagnosis are associated with poorer longer-term outcomes, by increasing the length of follow-up of the subgroup of patients who were recruited on the basis of having received a new diagnosis of CD (the "new diagnosis" cohort).

5.2 Objectives

5.2.1 Primary objective

To improve the prediction of disabling Crohn's disease (CD) within 5 years of diagnosis by developing and internally validating a multivariable prediction model using both existing clinical predictors and MRE-based CD severity scores

5.2.2 Secondary objectives

- To improve the prediction of disabling Crohn's disease (CD) within 5 years of diagnosis by developing and internally validating a multivariable prediction model using both existing clinical predictors
- To improve the prediction of disease phenotype at 5 years defined by the Montreal behaviour criteria by developing and internally validating alternative multivariable prediction models.
- To identify the specific combination of individual imaging findings that best predict disabling CD within 5 years of diagnosis

- To estimate the healthcare costs incurred within 5 years of a new diagnosis of CD and to explore patient, imaging and disease characteristics driving higher NHS costs

5.3 Trial Design

Development and internal validation of a multivariable model to improve prediction of disabling Crohn's Disease (CD) by incorporating imaging features in addition to known clinical predictors. We will use patients already recruited to the METRIC (Magnetic Resonance Enterography or Ultrasound In Crohn's Disease) study (ISRCTN03982913), HTA 11/23/01, and extend their follow-up from the current 6 months to a minimum of 4 years (average 5.3 years). New participants will be added to the retrospective cohort to achieve a sample size of 207 participants. No additional participant interventions are required.

6 Methods

6.1 Site Selection

The trial 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). All sites who participated in the HTA METRIC study (ISRCTN03982913) will be invited to participate in the METRIC-EF study. Some of these sites may have changed personnel since the initiation of the METRIC study, including the Principal Investigator (PI); a new PI will be selected for that site as per details provided in section 6.1.2. In addition, new sites who have expertise in MRE, as well as lead radiologists and gastroenterologists with specific expertise in IBD will be invited to participate in the METRIC-EF study.

6.1.2 Site/Investigator Eligibility Criteria

To participate in the METRIC-EF trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the METRIC-EF Sponsor and/or Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants and enter data
- Sites should be able to identify and consent previous METRIC patients who are eligible for METRIC-EF *(this is for METRIC participating sites only)*
- Sites should be able to identify patients with Crohn's disease who had their disease diagnosed at least 4 years prior to consensus meeting date.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, by provision of a CV, 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 who have been delegated significant trial 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 trial to enable them to conduct the trial 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 CCTU. This will be supported by central funding allocated to support site research nurse activity.

6.2 Site approval and activation

On receipt of the signed Statement of Activities and Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site activation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and which was given favourable opinion by the Ethics Committee (EC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at CCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

The study will focus on patients with a new diagnosis of Crohn's Disease, who were either (a) enrolled in the METRIC study ("METRIC cohort") or (b) imaged using MRE * as part of their routine care at diagnosis ("retrospective cohort").

**- patients whose eligibility was confirmed by SBUS (10 patients) as part of protocol V2.0 will be replaced and will no longer be eligible for primary end point analysis.*

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 trial 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 trial to ensure that the trial 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 trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

6.3.1.1.1 METRIC cohort

- Enrolled in the METRIC study, new diagnosis cohort AND
- Formed part of the final new diagnosis cohort (i.e. with a confirmed diagnosis of Crohn's disease and underwent relevant study interventions and follow-up)
- METRIC new diagnosis cohort inclusion criteria were:
    - Aged 16yrs or more
    - Newly diagnosed with Crohn's disease based on endoscopic, histological, clinical and radiological findings, OR
    - Highly suspected of Crohn's disease based on characteristic endoscopic, imaging and/or histological features but pending final diagnosis (only participants who ultimately were confirmed to have Crohn's disease will continue in this extension study)
- Have signed METRIC-EF consent form

6.3.1.1.2 Retrospective Cohort

- Aged 16yrs or more and received a new diagnosis of Crohn's disease based on endoscopic, histological, clinical and radiological findings
- Dedicated enteric imaging (MRE) acquired according to the standards of the METRIC study (see Section 6.4) and performed either <3months after, or <3months prior to the new diagnosis of Crohn's disease
- Institutional practice is to perform MRE in all patients with newly diagnosed Crohn's disease
- Has >4yrs clinical follow-up data, or anticipated to have such follow-up data by the time of consensus endpoint meetings (mid 2021; see Section 6.5.4) at recruiting hospitals

6.3.1.2 Participant Exclusion Criteria

6.3.1.2.1 METRIC cohort

- Enrolled in the METRIC study but not part of the final new diagnosis cohort

6.3.1.3 Co-enrolment Guidance

Patients will be potentially eligible for the METRIC-EF study even if recruited into another study. CI agreement should be sought prior to co-enrolment.

6.3.1.4 Screening Procedures and Pre-enrolment Investigations

Metric Cohort -

For participants who are part of the Metric cohort, written informed consent to enter into the trial will be sought, including explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific data is collected.

This study does not involve any additional patient interventions; instead, it requires that their clinical teams review routinely-held clinical data. Sites will either (a) explain the study in person, at a routine out-patient visit or (b) write to or (c) telephone all individuals, to notify them of the study and ask them to consent to the use of their information.

In the event that METRIC patients do not want to take part in the METRIC-EF study, their wishes will be respected, and their data will not be accessed. Such individuals will be replaced by expanding the size of the retrospective cohort.

The only procedures that may be performed in advance of informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

Every effort will be made to obtain consent from the METRIC cohort patients. If the patients in this cohort do not respond to site contact after a minimum of 2 contacts (Initial contact and 1 follow up contact after 2 weeks of initial contact if no response received) and passage of 4 weeks after follow up contact, then these patients can be registered as part of the Retrospective Cohort, as per the Retrospective Cohort guidelines. This will only apply if patients at the time of contact did not explicitly refuse consent. None of the data collected as part of the METRIC study for these patient will be used and CCTU will not be able to link these patient's METRIC-EF study ID to their original METRIC study ID.

If sites are unable to identify the METRIC cohort patients from information provided by CCTU (e.g. medical record or archiving issues), these patients will by default become part of the Retrospective cohort (as per Retrospective Cohort guidelines).

Retrospective Cohort

Pseudonymised data for patients eligible for this cohort can be collected and sent to the CCTU without obtaining prior consent for the following reasons:

- This study only requires routinely-collected clinical data without additional visits or interventions.
- CCTU will receive sufficiently pseudonymised data. The CRF will only collect study ID and no other participant identifiers. The study ID will remain at site and stored at CCTU.

This does not apply to the Metric cohort as the CCTU holds additional participant identifiers linked to personal data from the original Metric study.

The NIHR IBD BioResource team at Cambridge will provide assistance to site teams in identification of eligible participants by providing sites teams with eligible participants' IBD BioResource trial ID, NHS number, date of diagnosis and type of diagnosis. This data is available within NIHR BioResource from participants who have already consented to the NIHR BioResource study, and this data will be provided to the respective site teams in line with their existing permissions (NIHR BioResource Research Tissue Bank: 17/EE/0025 and IBD BioResource: 15/EE/0286). No data will be sent by NIHR IBD BioResource to CCTU.

6.4 MR image analysis

The study aims to determine if MRE parameters can predict subsequent disease course after new diagnosis. Each modality is able to depict a large number of different parameters that reflect different aspects of Crohn's disease biology. It is not possible to explore the potential prognostic significance of all of these different variables due to the loss of statistical power that would be incurred by using such a large number of predictors. Therefore, pre-existing validated Crohn's disease activity and bowel damage scores will be collated and will be calculated centrally at UCL (see below for further details).

6.4.1 Magnetic resonance imaging

6.4.1.1 Sequences

Images acquired in METRIC were required to adhere to a minimum sequence dataset. The same minimum sequences must have been acquired for the patients in the retrospective cohort, with the

exception of the diffusion-weighted imaging (DWI) which is not necessary for calculation of the relevant activity and bowel damage indices (see below).

Required	Optional
Coronal TrueFISP	Axial TrueFISP
Axial HASTE	Dynamic TrueFISP motility
Coronal HASTE	
Coronal HASTE with fat suppression	Axial HASTE with fat suppression
Axial DWI (b50 and b600)*	Additional b values
Coronal pre- and post-gadolinium VIBE (60-70 seconds)*	Axial post-gadolinium VIBE

**Optional for retrospective cohort*

For all sequences named above, the equivalent sequence variant according to different MRI manufacturers will be permitted.

***HASTE** = Half-Fourier Acquisition Single-shot Turbo spin Echo;*	***TrueFISP** = True Fast Imaging with Steady State Precession;*
***DWI** = Diffusion Weighted Imaging;*	***VIBE** = Volumetric Interpolated Breath-hold Examination.*
***Patient preparation**: Nil by mouth for 4 hours, then 1-1.5L oral contrast ingested over 40min prior to scan;*	*20mg Buscopan given unless contraindicated after initial planning sequences.*

6.4.1.2 Magnetic resonance Enterography Global Score (MEGS)

This is a validated score that encompasses aspects of both inflammatory activity and bowel damage, and has been validated against several standards of reference including a composite clinical reference[22], faecal calprotectin[23] and capsule endoscopy[24]. The score is calculated as follows: Each enteric segment (jejunum; proximal ileum; terminal ileum; caecum; ascending colon; transverse colon; descending colon; sigmoid colon; rectum) is scored separately, using the table below. The segmental score is then multiplied by a factor depending on the length of disease involvement in that segment. Finally, scores for extramural features are added, giving a total score (maximum possible = 296).

Mural features	0	1	2	3	Score
Mural thickness	<3mm	>3-5mm	>5-7mm	>7mm	a
Mural T2 signal (oedema)	Normal	Minor increase	Moderate increase	Large increase	b
Perimural T2 signal	Normal	Increased signal but no fluid	Small (≤2mm) fluid rim	Large (>2mm fluid rim)	c
Contrast enhancement: *amount*	Normal	Minor increase	Moderate increase	Large increase	d
Contrast enhancement: *pattern*	N/A or homo-genous	Mucosal	Layered		e
Haustral loss (colon only)	None	<1/3 segment	1/3 to 2/3 segment	>2/3 segment	f
Mural score for that segment		**a+b+c+d+e+f = g**			

Mural features	0	1	2	3	Score
Multiplication factor	**1**	**1.5**	**2**	**TOTAL SEGMENTAL SCORE g * multiplication factor**	
Length of disease in that segment	<5cm	5-15cm	>15cm		

Sum all segments, then add extramural score on a per-scan basis; 5 points for each of: (1) lymph nodes >1cm short axis, (2) comb sign (linear structures on the mesenteric border of an affected bowel segment), (3) abscess and (4) fistula.

6.4.1.3 Simplified Magnetic Resonance Index of Activity (sMaRIA)

This is a different MRI score that quantifies disease activity. It is a simplification of an older activity index that was validated against a endoscopic standard of reference[12], but was designed for use with a water enema to distend the colon, which is rarely done in normal practice internationally. The sMaRIA has also been endoscopically validated[25]. There is good evidence that improvements to the MaRIA score reflect mucosal healing[7] but it may be less able to predict longer-term disease outcomes[26]. It is calculated by scoring each enteric segment (jejunum; ileum; ascending colon; transverse colon; descending colon; sigmoid colon; rectum) using the table below. The global sMaRIA score is the sum of the individual segmental sMaRIA scores.

Feature	Description
Mural thickness	Binary: Measured in mm using software calipers, scored as abnormal if >3mm
Mural oedema	Binary: present if there is high signal intensity on T2 sequences with fat saturation, compared with normal-appearing loops
Fat stranding	Binary: present if there is loss of the normal sharp interface between the intestinal wall and mesentery, with oedema/fluid in the perienteric fat
Ulceration	Binary: present if mucosal surface has a deep depression, visible on 2 MRI sequences
sMaRIA score for that segment	**= 1 point for each of mural thickness, mural oedema and fat stranding; 2 points for ulceration (maximum 5 points per segment)**

6.4.1.4 Lémann Index (LI)

The Lémann index is designed to capture established bowel damage rather than acute activity. The score comprises several factors that can be assessed either clinically, using imaging or via endoscopy. For this study, we will use the imaging-derived score. The gastrointestinal tract is divided into four regions; upper tract, small bowel, colorectum and anus. Each is assessed for (a) surgical interventions (b) stricturing lesions and (c) penetrating lesions. Since the anal canal will not have been specifically imaged in METRIC, we will omit the scores for the anus. Each of the remaining three regions is assessed using MRI as a series of "segments" (corresponding to 20cm lengths of the small bowel or a colonic segment i.e. caecum, ascending, transverse, descending, sigmoid, rectum) and assigned a score according to the table below (only the imaging-scored variables have been included here). The segmental scores are adjusted by a co-efficient for that particular organ, and then summed to provide the complete Lémann index[27].

The database will be designed to calculate the score, based on an automated Excel spreadsheet that has been supplied by the lead author of the original publication (J Cosnes).

Surgical interventions†						
Organ	**Method of assessment**	**n***	**Segment**	**Grade 1**	**Grade 2**	**Grade 3**
Upper tract	History	3	Oesophagus, stomach, duodenum	-	Bypass diversion or stricturoplasty	Resection
Small bowel	History	20	Each 20cm SB segment	-	Bypass diversion or stricturoplasty	Resection
Colon / rectum	History	6	Each colonic segment	-	Stoma, bypass diversion or stricturoplasty	Resection

† *This information will be collated from the original METRIC records, although a relevant past surgical history will be very rare since included patients are, by definition, those with a new diagnosis of Crohn's disease.*

**n = number of segments within a particular organ*

Stricturing lesions						
Organ	**Method of assessment**	**n**	**Segment**	**Grade 1**	**Grade 2**	**Grade 3**
Upper tract	MRI	2	Stomach, duodenum	Wall <3mm; segmental enhancement without prestenotic dilatation	Wall thickening ≥3mm or mural stratification with no prestenotic dilatation	Stricture with prestenotic dilatation
Small bowel	MRI	20	Each 20cm SB segment	Wall <3mm; segmental enhancement without prestenotic dilatation	Wall thickening ≥3mm or mural stratification with no prestenotic dilatation	Stricture with prestenotic dilatation
Colon / rectum	MRI	6	Each colonic segment	Wall <3mm; segmental enhancement without prestenotic dilatation	Wall thickening ≥3mm or mural stratification with no prestenotic dilatation	Stricture with prestenotic dilatation or >50% of the lumen

Penetrating lesions						
Organ	**Method of assessment**	**n**	**Segment**	**Grade 1**	**Grade 2**	**Grade 3**
Upper tract	MRI	2	Stomach, duodenum	-	Deep transmural ulceration	Phlegmon or fistula
Small bowel	MRI	20	Each 20cm SB segment	-	Deep transmural ulceration	Phlegmon or fistula
Colon / rectum	MRI	6	Each colonic segment	-	Transmural ulceration	Phlegmon or fistula

6.4.1.5 Interpretation and blinding

MRE scans will be interpreted by one from a pool of METRIC-EF site radiologists; all are gastrointestinal radiologists and are experienced in use of MRE, both in clinical and research settings. Radiologists will be allocated a pool of MRE scans for scoring.. These will be interpreted blinded to all clinical information other than that relevant for the calculation of the relevant index (e.g. surgical history for Lémann index).

6.4.2 Central collection of study imaging data

Recruitment sites from METRIC have already sent full MRE datasets pseudoanonymised with the study number which have been loaded onto an online platform (Biotronics);. The central study team will complete retrieval of any outstanding MRE datasets from METRIC sites after study initiation (this may include site visits). For the retrospective cohort, imaging data will be transferred for central review using CD or DVD by posting pseudonymised discs to the Chief Investigator or using a secure electronic alternative [further details will be provided by the CCTU].

6.4.3 Protocol Discontinuation

Though participants in the METRIC cohort will have already consented to the METRIC study, they will be requested to sign a new consent form confirming their participation in the METRIC-EF trial

However, an individual may subsequently withdraw from the study if they choose to withdraw consent. 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. Only patients who have provided consent to either the METRIC or the Retrospective cohort will be able to withdraw consent.

For future participants entering as part of the retrospective cohort, their data will be collected without consent so this data will not be withdrawn.

6.5 Documentation and assessment of disease severity at follow-up

6.5.1 Time point of follow-up

Follow-up will be for a minimum of 4 years; since participants were recruited into METRIC over a 30 month period, this corresponds to an average length of follow-up of approximately 5.5 years. This provides sufficient time for clinically-important complications of Crohn's disease to manifest, since these tend to accumulate over time.

6.5.2 Primary definition of disabling disease

The primary definition of disabling disease will be a modified version of that initially described by Beaugerie et al[30]. The original definition has been modified to clarify some of the symptoms and to permit use of disease-modifying therapy, since this has become common as a preventative measure in modern practice. Disabling disease will therefore be defined as any of:

- Hospitalisation after diagnosis for CD flare or disease complication, as judged by the treating clinician
- More than 2 (i.e. 3 or more) corticosteroid courses and/or dependence on corticosteroids

- Any intestinal resection >50cm, or surgical operation for perianal disease (examination under anaesthesia without seton placement does not meet this criterion; abscess drainage and/or seton placement does)
- Chronic disabling symptoms, defined as a cumulative time of over 12 months, of one or more of:
    - Diarrhoea with nocturnal stools (getting up for a bowel movement after having gone to bed)
    - Urgency (defined as having to rush to the toilet for a bowel movement)
    - Abdominal pain due to intestinal obstruction (requires imaging confirmation or surgical proof)
    - Fever (documented tympanic temperature of >38.0°C or oral temperature of >38.3°C)
    - Fatigue (defined as not feeling full of energy)
    - Joint pain not due to an alternative cause (as judged by a suitably qualified healthcare professional)
    - Uveitis (confirmed by a suitably qualified healthcare professional)
    - Pyoderma gangrenosum (confirmed by a suitably qualified healthcare professional)

6.5.3 Alternative definitions of disabling disease

Since the Beaugerie criteria are imperfect, further definitions of adverse outcome in Crohn's disease will also be collected; specifically the Liège criteria[31] and Montreal behaviour criteria[32].

The Liège criteria are met if any of the following occur:

- Development of complex perianal disease
- Any colonic resection
- Two or more small bowel resections
- A single small bowel resection of >50cm
- Construction of a definitive stoma

Complex perianal disease is defined as per the American Gastroenterological Association, i.e. any of (a) an extra-, supra- or high trans-sphincteric or intersphincteric fistula ("high" = involving >1/3 of the length of the external sphincter for trans-sphincteric fistulas or origin above the dentate line for intersphincteric fistulas, (b) >1 external opening, (c) an anal or rectal stricture, (d) fistulation to the urogenital tract, (e) associated with active proctitis at endoscopy[33].

The Montreal behaviour criteria simply classify Crohn's disease as either inflammatory (B1), stricturing (B2) or penetrating (B3). Stricturing disease will be defined as a fixed luminal narrowing of >50% relative to normal proximal bowel. Penetrating disease will be defined as an intra-abdominal or enterocutaneous fistula, inflammatory mass or abscess. Perianal fistulas do not, in isolation, meet this criterion. The behaviour criteria must be confirmed by imaging, endoscopy and/or surgery.

6.5.4 Consensus panel assessment of disease severity

Consensus panels will be convened at each of the recruitment sites; the number of panel meetings will be determined by the number of participants recruited at each site. Panels will comprise, as a minimum, one gastroenterologist and one radiologist, aided by the site research nurse. Only people who are involved in patient care at that recruitment site will be present at the consensus meetings when these meeting(s) discuss participants in the retrospective cohort whose pseudonymised data will be provided to CCTU without obtaining prior consent.

The consensus panels will review all available clinical information, collated in advance by the research nurse. This will include investigations such as C-reactive protein, faecal calprotectin, endoscopy (conventional and capsule), imaging (MRI, ultrasound, CT, fluoroscopy), surgical and histopathological findings, clinical activity scores (e.g. Harvey-Bradshaw Index) and overall clinical course including outpatient and inpatient clinical records.

Using all of the available data, the consensus panels will record (a) the presence or absence of disabling disease, as defined in Section 6.5.2, (b) the presence or absence of other definitions of adverse outcome, as defined in Section 6.5.3, and (c) the date at which this endpoint was reached (for example, the date of the surgical resection meaning the participant fulfils the criteria for disabling disease).

6.6 Outcomes

6.6.1 Primary Outcomes

Comparative predictive ability of prognostic models incorporating MRI severity scores (MEGS, sMaRIA and Lémann index) to improve predictions from a model based on clinical characteristics alone to predict the development of disabling disease at 5 year follow-up.

6.6.2 Secondary Outcomes

1. Comparative predictive ability of prognostic models incorporating MRI severity scores (MEGS, sMaRIA, Lémann index) to improve predictions from a model based on clinical characteristics alone to predict the development of Montreal B2 / B3 disease or Liège severe disease at 5 year follow-up.
2. Identification of the best combination of individual MRE features for prediction of disabling Crohn's disease (all definitions) within 5 years of new diagnosis.
3. Average per-patient and national healthcare costs incurred within 5 years of a new diagnosis of Crohn's disease.
4. Patient, disease phenotype and imaging characteristics associated with higher economic costs within 5 years of diagnosis.

6.7 Loss to follow-up and closure

6.7.1 Patients no longer under routine follow-up

Some participants from the original METRIC study will no longer be under routine clinical follow-up at the time of the scheduled 5 year consensus panel meeting. If this is because of discharge from hospital care, all information up to the point of discharge will be collated once consent has been obtained from the patient and the patient will be discussed at the consensus panel meeting and their data used for the study outcomes. Sites will also be requested to obtain the patient's current disease status by contacting their GPs. Permission to obtain information from GP will be requested from the patient at the time of Informed Consent.

If, however, the participant exercises the view that they no longer wish to be followed up, this view must be respected and the participant will not be included in the METRIC-EF study. Additional participants will be added to expand of the retrospective cohort, to compensate for loss of statistical power.

For future Retrospective Cohort participants, only participants who have a minimum of 4 year of follow-up visits at recruiting hospitals will be deemed eligible for registration and GP(s) will not be contacted for additional information.

6.8 Trial Closure

For regulatory purposes, the end of the main study will be after the final consensus panel assessment has been completed for the final patient, all data queries closed and primary end point analysis completed. At this point, the "declaration of end of study" form will be submitted to the requisite ethical and governance committees.

6.9 Sample Size

6.9.1 Primary power

We propose including **207** participants newly diagnosed with CD: 131 from the METRIC prospective cohort, and a 76 participant retrospective cohort recruited from METRIC sites. The number of events and non-events is the crucial parameter for a prognostic study – in this case, occurrence of the modified Beaugerie definition of disabling Crohn's disease provided in Section 6.5.2. We anticipate this number will provide between 114 and 124 events (83 to 93 non-events); see assumptions in Section 6.9.1.1 below. The number of the retrospective cohort will be increased to meet the 207 participant target if recruitment to the METRC cohort is below 131.

6.9.1.1 Assumptions

We assume the prevalence of our modified Beaugerie definition of disabling disease (see Section 6.5.2) will be approximately 55-60%; this is primarily informed by the external validation cohort[31] of the Beaugerie descriptors, in which 57% of 361 participants developed disabling disease at 5 years. In support, we have performed local audit of 33 newly-diagnosed patients at one METRIC recruitment centre; 5 of 33 patients met the definition by mean 11.3 months = 16% at 1 year. Extrapolation to 5 years give 58% prevalence, similar to that expected from the literature[31]. We assume that the rate of development of disabling disease is approximately linear over time, by analogy with other definitions of adverse outcome in Crohn's disease (e.g. Fig 1, page 247 of reference[34]; Fig 1, page 950 of reference[31]).

Therefore, 207 participants provides 114 to 124 events (i.e. development of disabling disease) and 83 to 93 non-events (i.e. no such disabling disease); the smaller number is the more important when considering such a modelling study.

6.9.1.2 Adequacy of this number of events/non-events

Calculating sample sizes for prognostic studies suffers from the lack of readily applied methods suitable for all study designs, since it depends on whether the primary aim is to select variables suitable for inclusion in a new model, or to evaluate variables within a model with pre-specified, fixed variables. Here, we will test a small number of MRE scores in the context of a model using fixed variables. These fixed variables will be defined as per Section 6.13 Therefore, recommendations for sample sizes relevant to external validation are most appropriate. Accordingly, the literature suggests we require 80 to 100 events for model evaluation where variables are pre-specified and fixed[35]. This also provides sufficient power to assess whether addition of the 3 MRE scores enhance prediction, under the widely-used estimate of 10-20 events per variable[36].

6.9.2 Power for secondary outcomes

6.9.2.1 Other definitions of adverse outcome

The rate of Liège severe disease is estimated to be approximately 20% at 5 years, taken from the Kaplan-Meier plot presented in Fig 1, page 950 of reference[31]). Therefore, this provides approximately 41 events which is likely to be insufficient to construct meaningful prognostic models. Analysis for this endpoint will be descriptive only, unless our assumptions are incorrect, and sufficient events accumulate to permit model construction.

6.9.2.2 Identification of most important MRE and SBUS variables

Principal Component Analysis will be used to reduce a large number of individual imaging variables to ideally three eigenvector variables, that allow the most influential imaging features to be tested for their add-on effect to enhance a model based clinical characteristics alone.

6.10 Recruitment and Retention

6.10.1 Recruitment

METRIC-EF participants will be recruited from previous METRIC patients (newly-diagnosed cohort) and new participants with recent diagnosis of Crohn's disease (retrospective cohort).

6.10.2 Retention

Participants do not need to undergo any additional tests as part of this trial. Only data obtained as part of their routine clinical care will be collected. In the event of participants being lost to follow up at the participating sites, participant's GP will be contacted for routine clinical information, post consent (this is only applicable to Metric Cohort and those patients on Retrospective cohort who have provided consent).

6.11 Assignment of Participant Identification Numbers

Each participant will be given a unique trial Participant Identification Number (PIN). Sites will be provided guidance by CCTU on assigning trial ID to participants. This ID will be assigned once a consent form (METRIC Cohort only) has been received from the participant.

For Retrospective Cohort, sites will be able to register eligible participants after identification without obtaining prior consent.

The Registration CRF (online) has been set-up to ensure no identifiable information (initials or partial date of birth) will be collected for the Retrospective Cohort.

6.12 Data Collection, Management and Analysis

6.12.1 Data Collection Methods

Coded data will be collected from the trial sites using either paper or electronic Case Record Forms (CRFs) and transferred to CCTU. The data will be entered into the database either by a member of the METRIC-EF trial team or by a delegated member at site and stored on secure servers based at UCL. Training on CRF completion and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s).

Data collection, data entry and queries raised by a member of the METRIC-EF trial team will be conducted in line with the CCTU and trial-specific Data Management Standard Operating Procedure.

Subject Identification logs will be kept at the trial site in a locked cabinet within a secured room.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 2018.

6.12.2 Data Management

Data will be entered in the approved METRIC-EF database by a member of the trial team at CCTU or a delegated member at site and protected using established CCTU procedures.

Coded data: Participants will be given a unique trial Participant Identification Number (PIN). Data will be entered under this identification number onto the central database stored on the servers based at UCL. The database will be password protected and only accessible to members of the METRIC-EF trial 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.

The database and coding frames have been developed by the Clinical Trial Manager in conjunction. 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 trial the database will be retained on the servers of UCL for on-going analysis of secondary outcomes.

Sites participating in the original METRIC trial will be provided with original METRIC Participant Identification Number and date of consent for METRIC trial by the CCTU. This will aide in robust identification of participants especially at sites where the original METRIC trial has been archived.

As part of this trial, sites will need to maintain subject identification code list created for this trial. This will be held in written form in a locked filing cabinet. After completion of the study the subject identification log which will provide link for patient identification will be destroyed after end of all analysis on the METRIC-EF study .

6.13 Statistical Methods

6.13.1 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.

6.13.2 Statistical Methods – Outcomes

6.13.2.1 Primary Outcome

Comparative predictive ability of prognostic models incorporating MRI severity scores (MEGS, sMaRIA and Lémann index) to improve predictions from a model based on clinical characteristics alone to predict the development of disabling disease at 5 year follow-up.

- Development of multivariable prognostic model using clinical predictors. Clinical predictors pre-specified, and identified from the published literature[37,38] and the (in progress) HTA systematic review and associated analyses[39].

- Comparison of add-on effect of each MRI score (MEGS, sMaRIA and Lémann index) to developed model based on clinical predictors alone. Influence of MRI scores will be compared using the statistical significance of MRI in the prognostic models and net reclassification improvement for likely treatment alteration with MRI-based vs. standard models.
- Internal validation using bootstrap samples (sampling with replacement): at least 200 or more bootstrap samples until estimates remain stable.
- The full details of model selection and specification, thresholds for model evaluation, approach to missing data e.g. multiple imputation, methods for assumption checking, sensitivity analyses, internal validation, and assessment of model performance will be specified in the full Statistical Analysis Plan.
- The predictive ability of these models will also be reported for 1, 2 and 3 year predictions.
- Reporting of model development and predictive measures will adhere to the principles of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement[40].

6.13.2.2 Secondary outcomes

SECONDARY OUTCOME #1

Comparative predictive ability of prognostic models incorporating MRI severity scores (MEGS, sMaRIA, Lémann index) to improve predictions from a model based on clinical characteristics alone to predict the development of Montreal B2 / B3 disease or Liège severe disease at 5 year follow-up.

- Modelling will be conducted as for the primary outcome.
- Models will only be constructed if the number of events / non-events is adequate; if this is not achieved, only descriptive statistics will be provided.

SECONDARY OUTCOME #2

Identification of the best combination of individual MRE features for prediction of disabling Crohn's disease (all definitions) within 5 years of new diagnosis.

- Principal Components Analysis (PCA) to condense MRE parameters into a small number of Eigenscores (Eigenvector) variables
- This allows the most predictive individual imaging features to be tested as a small number of variables in predictive modelling.
- The statistical significance will then be tested via a parametric survival prediction model.
- Influential imaging features can be identified to allow further simplification of scores.

SECONDARY OUTCOME #3

Average per-patient and national healthcare costs incurred within 5 years of a new diagnosis of Crohn's disease.

- Hospital healthcare usage from health economic CRFs will be multiplied by unit costs of the relevant items, summed across the 5 year follow-up period, and averaged across the study population (median and mean).
- Mean costs per patient will be multiplied by the number of patients in the UK, stratifying by presence or absence of disabling disease, to estimate the cost-of-illness following diagnosis in the UK (both by UK incidence and prevalence).

SECONDARY OUTCOME #4

Patient, disease phenotype and imaging characteristics associated with higher economic costs within 5 years of diagnosis.

- Unadjusted annual and 5 year costs will be calculated separately according to presence vs. absence of disabling Crohn's disease, Liège and Montreal criteria, MRE parameters, treatments received, and patient demographic characteristics.
- Comparison between groups will be by one-way ANOVA and Mann-Whitney two-samples tests.
- Multivariable regression will be used to identify factors (Crohn's disease status, MRE parameters, treatments received, patient characteristics) associated with costs associated with higher costs.
- To account for skewness of the cost data, a generalised linear model with gamma family and log link will be used, experimenting with other distributional assumptions (log-normal, Gaussian, inverse Gaussian and negative binomial distributions), selecting that with best fit as judged by residual plots and the Akaike Information Criterion.
- A restricted version of the model will also be applied, only using data that are available at, and soon after diagnosis.

6.13.3 Economic evaluations

The health economic analysis will estimate the healthcare costs incurred within 5 years of a new diagnosis of Crohn's disease and investigate patient, imaging, treatment and other factors that drive these costs.

6.13.3.1 Health Economic Analysis

To estimate mean 5 year costs per patient, we require NHS hospital resource use data for all patients during the 5yr follow-up period. These will be collected in a similar manner to the original METRIC study, which captured similar costs but only for a 6 month period. A study-specific Case Report Form will capture hospital resource use data on the following cost components for each patient during follow-up: all imaging investigations; endoscopy; surgery; outpatient visits; inpatient stays; day cases; medications. These will be populated at each site by the relevant research team. Unit costs will be obtained from standard published sources, including NHS tariffs.

6.14 Data Monitoring

6.14.1 Data Monitoring Committee

As there are no interventions for participants as part of this study, the Data Monitoring Committee will be joint with the Trial Steering Committee (TSC) with the role of monitoring the quality and timeliness of the data received.

6.14.1.1 Safety reporting

As this is not an interventional study, no safety reporting is required.

6.14.2 Quality Assurance and Control

6.14.2.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the METRIC-EF trial 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 trial 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 trial 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 trial 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 trial related activities are fulfilled.

6.14.2.2 Central Monitoring at CCTU

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

6.14.2.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the METRIC-EF Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

6.14.2.3.1 Direct access to participant records

Metric Cohort

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

Retrospective Cohort

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to redacted source data and other trial related documentation for participants whose data has been provided to CCTU in pseudonymised format without prior consent.

Consent status of all participants will be maintained at CCTU and this will be provided to site and auditors / monitors at the time of visit to enable preparation of redaction of documents by site teams as required.

6.14.2.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions 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 trial oversight complies with the CCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the METRIC-EF QMMP.

6.14.2.4.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TT terms of reference.

6.14.2.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.14.2.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.14.2.4.4 Independent Data Monitoring Committee

As there are no interventions for participants as part of this study, the Data Monitoring Committee will be joint with the Trial Steering Committee (TSC) with the role of monitoring the quality and timeliness of the data received.

6.14.2.4.5 Trial Sponsor

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

7 Ethics and Dissemination

7.1 Ethics Committee Approval

Before initiation of the trial 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 EC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local permissions.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected without prejudicing their further treatment *(for Metric Cohort only and for those patients on Retrospective cohort whose consent has been obtained)*.

7.2 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.

7.3 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 in each country. A copy of the local permissions (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 randomised to the trial.

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

7.4 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.

7.5 Consent

Participants who are part of the Metric Cohort, will be provided with a Participant Information Sheet (PIS) and given time to read it fully. Participants will have the option of having a discussion regarding this study with a medically qualified investigator or suitable trained and authorised delegate either by phone or by coming into clinic. After satisfactory answers, if the participant is willing to participate, informed consent will be obtained. This can be done either by the participant signing the consent form in clinic or by signing it at home and posting it to the site team or photographing/ scanning the consent form and emailing it a member of the site team. Participants will also be provided with an option of completing an online consent form. It will be made completely and unambiguously clear in the participant information sheet that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

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 ethics committee prior to their use.

A copy of the approved consent form is available from the CCTU trial team.

Every effort will be made to obtain consent from the METRIC cohort patients. If the patients in this cohort do not respond to site contact after a minimum of 2 contacts (Initial contact and 1 follow up contact after 2 weeks of initial contact if no response received) and passage of 4 weeks after follow up contact, then these patients can be registered as part of the Retrospective Cohort, as per the Retrospective Cohort guidelines. . This will only apply if patients at the time of contact did not explicitly refuse consent. None of the data collected as part of the METRIC study for these patient will be used and CCTU will not be able to link these patient's METRIC-EF study ID to their original METRIC study ID.

If sites are unable to identify the METRIC cohort patients from information provided by CCTU (e.g. medical record or archiving issues), these patients will by default become part of the Retrospective cohort (as per Retrospective Cohort guidelines).

Retrospective Cohort

No consent will be required for this cohort as per reasons described in 6.3.1.4.2

IBD BioResource will help identify study participants with Crohn's disease in participating hospitals by providing the participating sites with participants' IBD BioResource trial ID, NHS number, Date of Diagnosis of Crohn's disease and method by which their Crohn's disease was diagnosed. This information will be provided by IBD BioResource to respective sites as this information was provided to IBD BioResource by sites after consenting participants. No data will be sent to CCTU directly by IBD BioResource. The EU General Data Protection Regulation (GDPR) and the UK Data Protection Act 2018 will be followed in this study.

Participant's identifiable data will be kept at the hospital site and no data will be received at the UCL CCTU/ lead team at UCLH unless it is sufficiently pseudoanonymised, i.e. study ID as the only identifier. Any data sent will use secure communication approved for such purposes by NHS data protection emails (e.g. secure NHS email such as NHS.net). UCL CCTU will preserve participants' confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored in a secure manner. The study will be registered in accordance with the EU General Data Protection Regulation (GDPR) and the UK Data Protection Act 2018 with the Data Protection Officer at UCL.

7.6 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 trial.

Stuart Taylor undertakes paid research consultancy for Robarts Clinical Trials. Andrew Plumb has provided paid educational lectures for Actavis, Acelity, Dr Falk, Janssen-Cilag, Takeda and Warner Chilcott.

7.7 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. 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 trial 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 Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial 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.

7.8 Finance

The METRIC-EF study is fully funded by the National Institute for Health Research (NIHR) via the Health Technology Assessment Programme (HTA 15/59/17) It is not expected that any further external funding will be sought.

7.9 Archiving

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

7.10 Access to Data

Requests for access to trial 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.

7.11 Publication Policy

7.11.1 Trial 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 will be provided to the National Institute for Health Research, Health Technology Assessment programme, and published in their journal. Data will be pseudonymous during the study; only fully anonymised data will be published, without any identifiers. Consented participants 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.

7.11.2 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 METRIC-EF 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).

7.11.3 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 METRIC-EF study data access plan.

8 Protocol Amendments

This is Version 4.0. This protocol has been amended as follows

Protocol Version	Major changes from prior version	REC substantial amendment?
4.0	• Extension of end date to 31Dec2022 to allow the sites and CCTU extra time to complete consensus meetings and data collection, cleaning and analysis	No
3.0	• Patient eligible for METRIC-EF only if diagnosis confirmed by MRE and not SBUS • Patients whose eligibility was confirmed previously by SBUS will be replaced • Secondary objectives related to SBUS deleted • METRIC cohort patients eligible for Retrospective cohort registration if signed consent form not received or site unable to identify patients from data provided by CCTU	Yes
2.0	• Pseudonymous data to be provided to CCTU at UCL without prior consent for the Retrospective Cohort post approval and implementation of METRIC_EF Protocol V2.0. At the time of monitoring and / or audit, patient records of future participant's in this cohort will be redacted prior to monitoring / auditing. • NIHR IBD BioResource team at Cambridge will assist METRIC-EF participating sites in indentifying potential patients by providing site teams with patient's IBD BioResource study ID, NHS Number, date of Crohn's disease diagnosis and how Crohn's Disease was diagnosed. • Simplified Magnetic Resonance Index of Activity (sMaRIA) will replace Magnetic Resonance Index of Activity (MaRIA) for disease activity quantitation. • subject identification logs will be destroyed at sites after completion of data analysis	Yes

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