METRIC (MR Enterography or ulTRasound In Crohn's disease)

Diagnostic accuracy for the extent and activity of newly diagnosed and relapsed Crohn's disease: a multicentre prospective comparison of magnetic resonance enterography and small bowel ultrasound compared to a reference standard in those aged 16 and over

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Sponsor	University College London (UCL)
UCL Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2012/008
REC	13/SC/0394

Authorisation: Chief Investigator

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Role	Deputy Director
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Date	

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1 Administrative information

This document was constructed using the UCL Comprehensive Clinical Trials Unit (CCTU) Protocol template Version 2.0. It describes the METRIC (MR Enterography or ulTRasound In Crohn's disease) trial, sponsored by UCL and co-ordinated by UCL 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, intervention, 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 UCL CCTU.

UCL 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 CCTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials (Chan AW 2013). The SPIRIT Statement Explanation and Elaboration 2013 (Chan AW 2013)can be referred to 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 UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable) and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and UCL CCTU.

Participating sites will inform UCL CCTU as soon as they are aware of a possible serious breach of compliance, so that UCL 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 trial to UCL CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the Director, UCL CCTU, or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN ISRCTN03982913 REC 13/SC/0394 CTU 2012/008
Date of Registration in Primary Registry	05 November 2013
Secondary Identifying Numbers	Other identifiers besides the trial identifying number allocated by the primary registry, if any. These include: • The Universal Trial Number (UTN) • Identifiers assigned by the sponsor (Trial Prioritisation Committee number) CTU/2012/008 • Other trial registration numbers issued by other registries (both primary and partner registries in the WHO Registry Network, and other registries) • Identifiers issues by funding bodies, collaborative research groups, regulatory authorities, ethics committees, institutional review boards etc.
Source of Monetary or Material Support	NIHR Health Technology Assessment
Primary Sponsor	University College London
Secondary Sponsor	Sponsor responsibilities for Trial Management are delegated to UCL CCTU. Responsibilities for trial management, trial oversight and database development are delegated to UCL CCTU. This is not a clinical trial of an Investigational Medical Product. No drug related management is required. Safety of patients will be managed but full pharmacovigilance is not required.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Professor Stuart Taylor (Chief Investigator) Email address: stuart.taylor1@nhs.net Telephone contact number: 07960 169 321 Postal address: Level 2 Podium, University College London Hospital, 235 Euston Road, NW1 2BU
Public Title	A comparison of Medical Resonance Imaging and Ultrasound techniques for diagnosing small bowel disease.
Scientific Title	Diagnostic accuracy for the extent and activity of newly diagnosed and relapsed Crohn's disease: a multicentre prospective comparison of magnetic resonance enterography and small bowel ultrasound compared to a reference standard in those aged 16 and over.
Countries of Recruitment	UK
Health Condition(s) or Problem(s)	Crohn's Disease: Patients who are newly diagnosed (within 3

Studied	months), or those with suspected luminal relapse.
Intervention(s)	• Magnetic Resonance Enterography (MRE) is a medical imaging technique, which relies on an electromagnetic field and electromagnetic radiation, to visualize internal structures of the body in detail. A patient firstly drinks liquid, to make the bowel easier to view and to distend it, before the patient undergoes the Magnetic Resonance scan. A dye contrast is administered intravenously during the course of the scan • Ultrasound Scanning is an alternative medical imaging technique, which uses sound waves to produce images of the internal organs, vessels and tissues. • There will be no control arm to this study. Patients will undergo both MRE and Ultrasound scanning. The resulting images will be compared to establish which medical imaging technique provides the information necessary for a better diagnosis. The results of the MRE and USS scans will be evaluated against the results of more commonly used, concomitant diagnostic tests that the patient will receive as part of their usual care.

Key Inclusion and Exclusion Criteria	**Inclusion criteria for participant selection:**
	
	Patient inclusion criteria; new diagnosis
	• Patients (≥ 16 years) undergoing or having undergone colonoscopy and either
	  ○ Newly diagnosed (within 3 months) 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.
	• Patient must be able to provide written informed consent.
	
	Patient inclusion criteria; suspected relapse
	• Patients (≥16 years) with a known diagnosis of Crohn's disease with high clinical suspicion of luminal relapse indicating radiological investigation
	  ○ High clinical suspicion defined as objective markers of inflammatory activity (raised CRP >8 mg/l OR raised calprotectin >100), or symptoms suggestive of luminal stenosis (including obstructive symptoms such as colicky abdominal pain, vomiting) OR

	abnormal endoscopy suggesting relapse. • Patient must be able to provide written informed consent. **Exclusion criteria for participant selection:** Patient exclusion criteria; all patients • Any psychiatric or other disorder likely to impact on informed consent • Evidence of severe or uncontrolled systemic disease which make it undesirable for the patient to participate in the study • Pregnancy • Contraindications to MRE (e.g. cardiac pacemaker, severe claustrophobia, inability to lie flat. Patient exclusion criteria; new diagnosis • Final diagnosis other than Crohn's disease • Patients undergoing surgical resection prior to colonoscopy
Study Type	This is a multicentre, non-randomised, single-arm, prospective comparison study. The radiologists conducting study specific imaging will be blinded to patient clinical data.
Date of First Enrolment	December 2013
Target Sample Size	334: 167 patients with a newly confirmed diagnosis and 167 patients with clinically suspected disease relapse
Primary Outcome(s)	Difference in sensitivity per patient of MRE and USS as diagnostic tests for the correct identification and localisation of small bowel Crohn's disease. • Ability to detect presence of disease (both active and inactive disease) • Sensitivity for each test is measured against a reference standard by consensus panel review at or after 6 months. Reference standard includes tests as available from clinical pathway including: ileo-colonoscopy, capsule endoscopy, imaging, histopathology, HBI, CRP, calprotectin including post therapy follow up. • Subgroup analysis for separate population of new versus relapse patients
Key Secondary Outcomes	1. Difference in specificity of MRE and USS for correct identification and localisation of small bowel Crohn's disease per patient. • Additional analyses will include extension to include both small bowel and colonic Crohn's disease for per patient analysis of (i) the difference in sensitivity and (ii) difference in specificity • Subgroup analysis for separate populations of new versus relapse patients 2. Comparison of USS and MRE to detect patients with active small bowel Crohn's disease

	(i) Difference in sensitivity and specificity per patient (ii) Difference in sensitivity and specificity of terminal ileum segment in subgroup of patients based on colonoscopic reference (iii) Additional analysis in colonic Crohn's for patients with colonoscopic reference for (a) Difference in sensitivity and specificity per patient (b) Difference in sensitivity and specificity of colonic segments • Subgroup analysis for separate populations of new versus relapse patients 3. Comparison of USS and MRE diagnostic accuracy to detect presence of disease (either active or inactive) (i) Difference in sensitivity and specificity per patient in small bowel and colonic Crohn's disease (ii) Difference in sensitivity and specificity of terminal ileum segment in subgroup of patients undergoing colonoscopy in small bowel and colonic Crohn's disease (iii) Difference in sensitivity and specificity per segment in subgroup of patients undergoing colonoscopy in colonic Crohn's • Subgroup analysis of (i) and (ii) in patients with small bowel only • Subgroup analysis for separate populations of new versus relapse patients 4. Comparative impact of MRE and USS on clinician diagnostic confidence for the presence of Crohn's disease and influence on patient management, to each other and to conventional imaging • Subgroup analysis for separate populations of new versus relapse patients 5. The lifetime incremental cost and cost-effectiveness of assessment using MRE and USS compared to each other, and to conventional imaging. 6. Diagnostic accuracy and radiologist confidence using hydrosonography compared to conventional USS 7. Comparative patient experience of MRE and USS. 8. Diagnostic impact of novel MRE sequences, notably diffusion weighted imaging on disease detection, diagnostic confidence and disease activity assessment 9. Inter-observer variation in the evaluation of MRE and USS datasets by radiologists, and to assess the impact of diagnostic confidence on accuracy

1.4 Roles and responsibilities

1.4.1 Protocol contributors

Name	Affiliation	Role
Professor Stuart Taylor	UCLH	Chief Investigator
Zainib Shabir	UCL CCTU	Clinical Project Manager
Dr Rinat Ezra	UCL CCTU	Former Trial Manager
Dr Sue Mallet	Oxford	Statistician
Laura Vallejo-Torres	UCL CCTU	Health Economist

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
UCL	UCL	Sponsor
HTA	NHIR	Funder

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Zainib Shabir	CCTU, UCL	Clinical Project Manager
Jade Dyer	CCTU,UCL	Trial Manager

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Stuart Taylor	UCLH	Chief Investigator
Steve Halligan	UCLH	Radiologist
Stuart Bloom	UCLH	Gastroenterologist
Simon Travis	Oxford	Gastroenterologist
Anthony Higginson	Portsmouth	Radiologist
Arun Gupta	St Mark's	Radiologist
Damian Tolan	Leeds	Radiologist
Ian Zealley	Ninewells	Radiologist
Andrew Slater	Oxford	Radiologist
Peter Wylie	Royal Free	Radiologist
Richard Pollok	St Georges	Gastroenterologist
Ilan Jacobs	General Electric Global Operations	Patient Representative
Sue Mallett	Oxford	Trial Statistician
Gauraang Bhatnagar	UCLH	Research Fellow
Rachel Baldwin	St Mark's	Research Radiologist
Zainib Shabir	UCL CCTU	Clinical Project Manager
Jade Dyer	UCL CCTU	Trial Manager

1.4.5 Trial Steering Committee

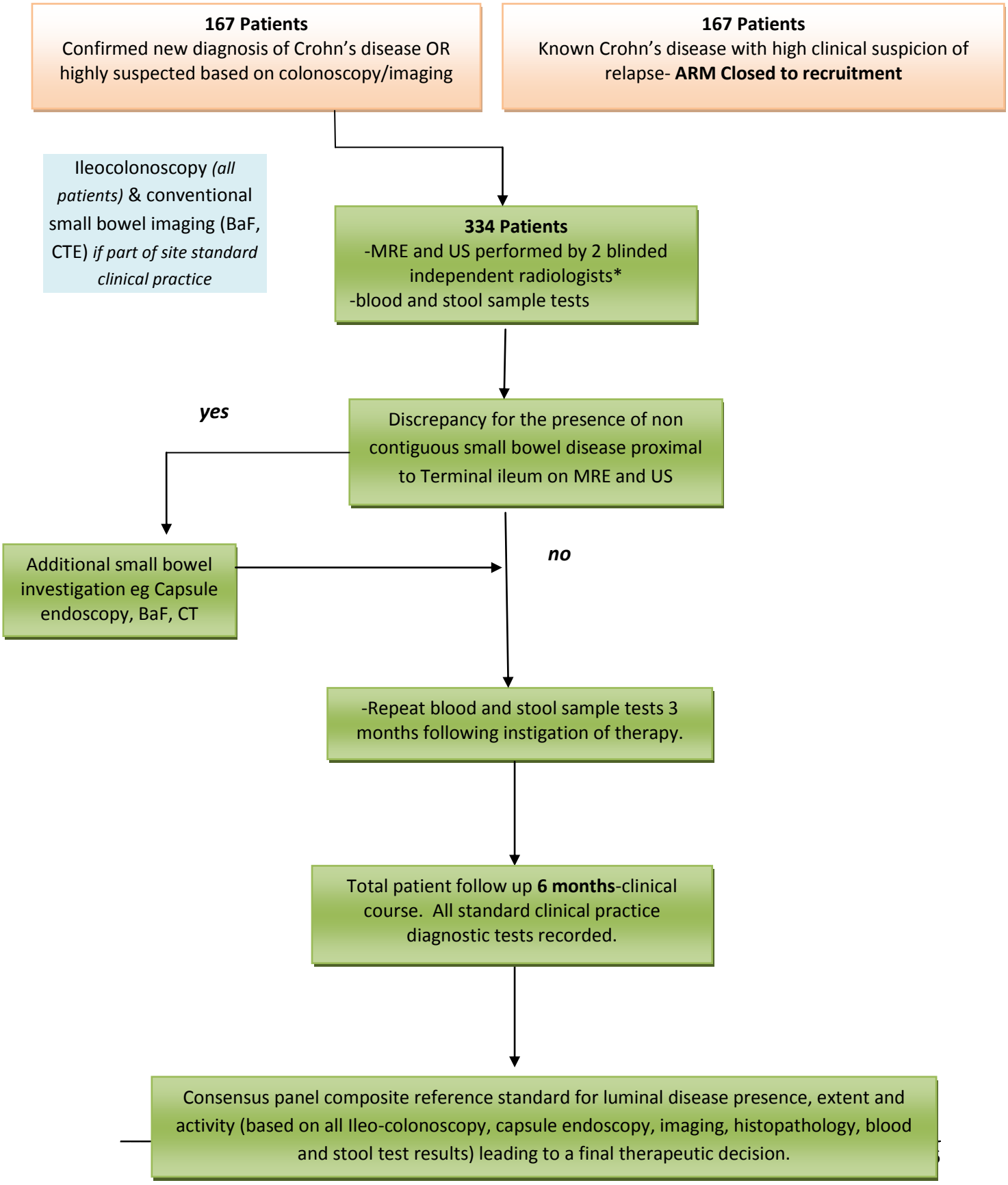
Name	Affiliation	Role and responsibilities
Vicky Goh	Kings College	Chair, Radiologist
James Lindsay	Barts, London	Gastroenterologist
Andrea Marshall	Warwick	Independent Statistician
Ilan Jacobs	General Electric Global Operations	Public Representative

1.4.6 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Tim Orchard	Imperial College	Chair, Professor of Gastroenterology
Mu Koh	Royal Marsden	Radiologist
Chris Rogers	University of Birmingham	Independent Statistician

2 Trial Diagram

2.1 Flow Diagram



** IF MRE already performed pre recruitment-blinded radiologist review*

2.2 Schedule of Assessments

	Time Period				
	-4 weeks to 0	**Consent 0**	**0-3 weeks**	**3 months**	**6 months**
Imaging					
MRE	**X***		**X**		
USS	X		**X**		
Clinical Tests					
Stool sample*	X		**X**	**X**	
Blood Sample*	X		**X**	**X**	
Colonoscopy**	X				
Abdominal Examination*	x		**X**	**X**	
Harvey Bradshaw Index*	x		**X**	**X**	
Questionnaires					
Test Experience (x2)			**1st to be completed on day of MRI scan & on D2 post scan**	**2nd will be completed post all imaging tests of bowel**	
QOL (x3)			**X**	**X**	**X**
Resource Use Diary (daily)			**Daily completion from 0-6 months**		

** IF MRE already performed within 4 weeks pre recruitment-the data can be used for study purposes, once reviewed by blinded radiologist*

*** if within3 weeks of MRI or USS used for the trial*
**** Colonoscopy already performed within 6 months prior to consent can be used in the case of new diagnosis.*

3 Abbreviations

AE	Adverse Event	**MoU**	Memorandum of Understanding
AR	Adverse Reaction	**MRE**	Magnetic Resonance Enterography
BaF	Barium Fluoroscopy	**MRI**	Magnetic Resonance Imaging
BSGAR	British Society of Gastrointestinal and Abdominal Radiology	**NAE**	Notifiable Adverse Event
CDR	Clinical Data Repository	**PACS**	Picture Archiving and Communications System
CI	Chief Investigator	**PI**	Principal Investigator
CRF	Case Report Form	**PIS**	Participant Information Sheet
CRP	C-Reactive Protein	**PSS**	Personal Social Services
CT	Computerised Tomography	**QA**	Quality Assurance
CTE	Computed Tomography Enterography	**QALY**	Quality of Life Year
CCTU	Comprehensive Clinical Trials Unit	**QC**	Quality Control
DSUR	Development Safety Update Report	**QMP**	Quality Management Plan
EU	European Union	**SPC**	Summary of Product Characteristics
FDA	(US) Food and Drug Administration	**SSA**	Site Specific Assessment
FRCR	Fellows of the Royal College of Radiologists	**SUSAR**	Suspected Unexpected Serious Adverse Reaction
FWA	Federal Wide Assurance	**TMF**	Trial Master File
GCP	Good Clinical Practice	**TMG**	Trial Management Group
HAI	Histological Activity Index	**TMT**	Trial Management Team
HBI	Harvey Bradshaw Index	**TNFα**	Tumour Necrosis Factor-Alpha
IBD	Inflammatory Bowel Disease	**ToR**	Terms of Reference
ICER	Incremental Cost-Effectiveness Ratio	**TSC**	Trial Steering Committee
ICH	International Conference on Harmonisation	**UCL**	University College London
IDMC	Independent Data Monitoring Committee	**US**	Ultrasound
IMP	Investigational Medicinal Product	**USS**	Ultrasound Scan
IRB	Institutional Review Board		
ITT	Intention to Treat		
MHRA	Medicines and Healthcare products Regulatory Agency		

4 Glossary

Barium Fluoroscopy (BaF) is a diagnostic tool used to evaluate the structure and function of the gastrointestinal tract, including the oesophagus, stomach and small bowel. A patient swallows barium (or barium is infused through a naso-jejunal tube), which coats the walls of the digestive tract, allowing the structure of the digestive tract to be outlined on an X-ray.

Calprotectin is a protein excreted in faeces, the levels of which rise in response to inflammation and are 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.

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.

Computerised Tomography (CT) is a medical imaging procedure that utilizes computer-processed X-rays to produce images of specific areas of the body. These cross-sectional images are used for diagnostic and therapeutic purposes in various medical disciplines.

Conventional Imaging is a term to describe standard imaging techniques used widely throughout the NHS. Examples include barium fluoroscopy, CT scanning and plain X-Rays.

C-Reactive Protein 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 sequence which detects the movement of water in tissues. 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 a fibre optic camera. Includes gastroscopy, colonoscopy and flexible sigmoidoscopy.

Fistulae is an abnormal connection or passageway between two epithelium-lined organs or vessels that normally do not connect.

Harvey-Bradshaw Index 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.

Hydrosonography entails filling the intestinal tracts with fluid, either by oral administration or by direct instillation of water or a non-absorbable solution (e.g., polyethylene glycol [PEG] solution) into the intestinal lumen by a nasojejunal tube, before sonographic examination.

Inflammatory Bowel Disease 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**.**

Luminal Relapse is the re-occurrence of inflammation affecting the tube of the gastrointestinal tract. Can affect anywhere from the mouth to the rectum in Crohn's disease.

Luminal Stenosis is an abnormal narrowing in a blood vessel or other tubular organ or structure. In the context of Crohn's disease, used to described reduction in caliber of the tube of the gastrointestinal tract.

Magnetic Resonance Imaging is a medical imaging technique used in radiology to visualize internal structures of the body in detail by applying magnetic energy.

Meta-analysis is a statistical method used to combine the results of several similar scientific studies to provide an overall summary of the results

Prospective cohort study is a cohort study that follows over time a group of similar individuals who differ with respect to certain factors under study, to determine how these factors affect rates of a certain outcome.

Scintigraphy is the production of two-dimensional images of the distribution of radioactivity in tissues after internal administration of a radioactive imaging agent, the images being obtained by a specialised camera.

Stricture is an abnormal narrowing of a duct or passage. In the context of Crohn's disease, describes a fixed narrowing in the lumen of the gastrointestinal tract.

Ultrasound Scanning is a medical imaging technique which produces images of the body by applying sound waves, usually via hand held probe in contact with the skin of the subject. It does not involve the use of X-Rays.

5 Introduction

5.1 Background and Rationale

Incidence of Crohn's disease and importance of radiological staging: Crohn's disease is a chronic inflammatory bowel disease, predominately affecting the young (most diagnosed < 25 years) and requiring lifelong medical and surgical therapy. It affects 150,000 people in the UK (around 1 in 700). According to a recent UK audit, inflammatory bowel disease accounts for 0.3% of work absenteeism, costs £115M in lost productivity and accounts for 27,000 hospital admissions annually (Leiper K 2006). Regular dedicated clinics are needed to manage this large patient cohort. The small intestine and/or colon are most commonly affected, complications including strictures, fistulae and abscesses. Diagnosis is made on a combination of clinical features, endoscopic, histopathological, biochemical and imaging findings. Radiological imaging is pivotal because the small bowel is relatively inaccessible to conventional endoscopy. Imaging defines disease presence, extent, biological activity and complications and is vital for timely and efficacious management.

Imaging provision: Approximately 100,000 NHS small bowel imaging investigations are performed each year, mainly in the investigation of suspected or known inflammatory bowel disease. Barium fluoroscopy (BaF) and Computerised Tomography (CT) are currently the standard investigations, but both impart a significant radiation dose, which is concerning given that Crohn's patients are young and need repeat imaging over several years; a recent audit found 15.5% of patients received a cumulative radiation dose that increased cancer risk by 7.3% (Desmond et al, 2008). Ultrasound (USS) is a safer alternative but requires operator expertise and may fail to adequately image the whole small bowel (Bozkurt T 1994); (Fraquelli M 2005). Magnetic resonance imaging (MRI) is increasingly advocated (Rieber A 2000); (Schunk K 2000), and magnetic resonance enterography (MRE) of the small bowel after distension with oral contrast, currently has significant but patchy uptake in the NHS. According to a UK survey (Hafeez R 2011), 90% of NHS radiology departments routinely perform BaF to investigate patients with known or suspected Crohn's disease, 80% perform CT, 56% perform USS and 38% perform MRI. Across the NHS there is *ad hoc* provision and utilisation of newer imaging technologies in Crohn's disease, with little consistency between hospitals and no coherent implementation strategy. This is likely due to a combination of limited MRI resources, limited direct diagnostic accuracy studies between MRE, USS and BaF, and limited training in interpretation of MRE amongst NHS radiologists.

Current literature: To date there have been three systematic reviews concerning the diagnostic accuracy of imaging tests in the diagnosis and staging of Crohn's disease. All have highlighted marked heterogeneity in the available literature, with most studies being single centre and including relatively small patient numbers. Variation in the applied standard of reference between studies is also apparent.

The first systematic review compared the accuracies of USS, MRI, scintigraphy and CT (Horsthuis K 2008)**.** Thirty three studies, from a search yielding 1406 articles were included in a meta-analysis but their quality was generally poor - all were single-site, un-randomised comparisons against a variable reference standard based on a combination of endoscopy, barium fluoroscopy and surgery. Two-thirds included fewer than 40 patients. Mean diagnostic sensitivity estimates on a per-patient basis were not significantly different between imaging modalities (89.7%, 93.0%, 87.8%, and 84.3% for USS, MRI, scintigraphy and CT, respectively). For detection of small bowel disease, MRI achieved 93% sensitivity and USS, 88%. There is evidence that USS sensitivity may be inferior to MRI for detecting proximal small bowel Crohn's disease which is further explored in the assumptions underlying the study power calculation. The authors of this systematic review confirm there is, however, insufficient data to perform a meta-analysis of test performance for the proximal and distal small bowel independently. A second systematic review from the same group reported the ability of MRI to assess the biological activity of Crohn's disease (Horsthuis K 2009) . A total of 7 studies including 140 patients were considered and MRI achieved 92% sensitivity for "frank" activity, 62% for mild activity and 62% for those in remission.

The third systematic review (Panés J 2011), included a total of 68 publications and compared the diagnostic performance of CT, MRI and USS for diagnosis, disease extent and disease activity classification. A formal statistical meta-analysis was not performed, the authors instead providing summary sensitivity and specificity figures, weighted for the number of patients in each included study. The overall diagnostic sensitivity of USS was between 75 and 93% and for MRI between 77 and 91%. Specificity was between 98 and 100% (USS) and 60 and 100% (MRI). Panes *et al* also considered the diagnostic ability of MRI and USS for assessing disease activity; headline USS sensitivity and specificity for detecting active disease was 85% (range 63-100%) and 91% (range 77-100%) respectively. Corresponding figures for MRI were 80% (range 55-100%) and 82% (range 46%-100%) respectively. In terms of extra-enteric complications, pooled sensitivity for USS detection of intra-abdominal fistulae was 74%, for MRI 76% and for intra-abdominal abscess detection pooled

sensitivity was 84% for USS and 86% for MRI. By way of comparison, the sensitivity and specificity of BaF for the diagnosis of Crohn's disease is 85%-95% and 89%-94% respectively.

Ultimately, the optimal imaging strategy for Crohn's disease remains uncertain and single centre data is confused. The choice of investigation in the NHS currently depends on rather nebulous reasoning including clinician personal preference, perceived costs, available infrastructure and radiological expertise. Unbiased data to inform the implementation strategy for newer imaging technologies is currently unavailable.

5.2 Study Objectives

Primary objective

The primary objective is to compare diagnostic accuracies of MRI and Ultrasound Scanning for the detection of small bowel Crohn's disease, and grading of inflammatory activity.
Sensitivity for each test is measured against a consensus reference standard. This means that the results from any other tests, all of which will be tests that are commonly used to detect and diagnose Crohn's disease, will be collated in order to provide a comparison for the Ultrasound and MRI results. The other tests include other types of imaging, as well as investigations (for example, blood tests) and examinations.

Secondary objectives

Secondary objectives are to compare diagnostic accuracies of MRI and Ultrasound Scanning for the detection of colonic Crohn's disease, and grading of inflammatory activity

There will also be separate analysis of the results of the two groups of patients: those who are newly diagnosed and those who are suffering a relapse. This will include the sensitivity and specificity from patient to patient and between the two groups.

For those patients undergoing colonoscopy as part of their clinical care, the findings on the MRI and USS scan will be compared with this colonoscopic reference for colonic segments and the terminal ileum.

Other questions to be addressed by this research are as follows:

- How the impact of on clinician diagnostic confidence and patient management compares between that based on Magnetic Resonance Imaging, Ultrasound and conventional imaging methods.

- Cost effectiveness of Magnetic Resonance Imaging and Ultrasound compared to each other, and to conventional imaging methods.

5.3 Trial Design

This is a multi-centre prospective cohort study comparing the diagnostic accuracy of MRE and USS for the presence, extent and activity of small bowel Crohn's disease. Trial framework is to detect superiority of MRE over USS.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to UCL 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) will be utilised, ensuring appropriate imaging expertise for the purposes of this study.

6.1.2 Site/Investigator Eligibility Criteria

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

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

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the METRIC Investigator Site File (ISF) documentation to use when applying for Site-Specific Approval (SSA).

Recruitment site eligibility will be assessed via Site Specific Information forms and local R&D approval sought. All documentation related to each site will be stored in the Trial Management File and copies of site specific information, filed in the Investigator Site File, at site. Study specific site eligibility factors are as follows: NHS hospital setting with lead radiologist affiliated to the British Society of Gastrointestinal and Abdominal Radiology (BSGAR) and with an established inflammatory bowel disease (IBD) practice (>150 patients seen annually)

- Experience in performing and interpreting enteric MRE and USS
- Access to conventional small bowel imaging techniques (barium fluoroscopy, CT)
- Agreement of identified imaging department, to allocate study specific appointments in order to perform MRE and USS within 21 days of patient recruitment
- Agreement of at least 2 participating radiologists (or 1 radiologist and one appropriate trained sonographer) and a gastroenterologist to take responsibility for ensuring adherence

to study protocol and Good Clinical Practice, and of site PI to ensure all required protocols are being followed

- IBD service core members have agreed to support the study, (e.g. in the identification of eligible patients) agreed to comply with the study protocol, and agreed to liaise with other members of the METRIC clinical research team.
- Agreement to adhere to trial protocols for image acquisition, blinded reporting, quality assurance processes, sharing of imaging data and reports and administrative/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 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, familiarity with the appropriate study imaging, 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 relevant qualifications and training of site staff delegated by the PI, with 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 UCL CCTU.

6.2 Site approval and activation

Written confirmation of site participation will be sent from the TMG to the PI, upon receipt of the signed Clinical Trial Agreement or Investigator Agreement, approved delegation of responsibilities log and staff contact details. The trial manager or delegate will notify the PI in writing of the plans for site initiation.

The site must conduct the trial 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 trial team at UCL CCTU.

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

6.3 Participants

6.3.1 Eligibility Criteria

The trial will recruit from two defined patient cohorts

1. Newly diagnosed Crohn's disease patients (diagnosis within 3 months of baseline)
2. Those with previously confirmed Crohn's disease with a high clinical suspicion of luminal relapse, requiring radiological investigation- please note this arm is now closed to any more recruitment.

New diagnosis

Ileo-colonoscopy is the most robust standard of reference for the diagnosis of colonic and terminal ileal Crohn's disease and will have been undertaken in all recruited patients as part of standard clinical practice. Some patients will have been diagnosed with Crohn's disease based on ileo-colonoscopic, histological and small bowel radiological investigations, prior to recruitment. A proportion of patients are provisionally diagnosed with Crohn's disease with high confidence based on typical endoscopic appearances, with a "final" diagnosis being made once the clinician is in receipt of all histological, biochemical and radiological findings. Alternatively, a diagnosis of "highly likely Crohn's disease" can be made based on typical imaging appearance (for example strictured, ulcerating terminal ileal disease as visualized following a barium fluoroscopy).

Patients with typical endoscopic or imaging findings of Crohn's disease are eligible for recruitment prior to completion of all additional investigations and final diagnosis. This will allow better control of the subsequent small bowel imaging investigations, and in particular facilitate blinding of radiologists interpreting MRE and USS, reducing the need to repeat tests or for central radiological review.

It is recognised that this approach may lead to a small number of patients who ultimately do not have Crohn's disease being recruited into the study and undergoing an additional procedure. This possibility will be taken into account in information given to the patients. Since the risks associated with MRE and USS are low, and will be fully explained to the patient, it is reasonable and ethical to

include such patients. They will by definition have evidence of abnormal bowel so in fact it is unlikely the additional tests will be truly superfluous. Patients initially recruited to the trial but subsequently not diagnosed with Crohn's disease will be replaced. They will be subsequently managed according to standard clinical care at the recruitment site. Delaying recruitment until after a final diagnosis would hinder the diagnostic pathway and therefore fail to mirror current clinical practice which rewards accelerated diagnosis.

Suspected relapse-

Arm closed to new recruitment as it has now reached it target of 167 participants as of November 2015, so please do not contact or provide any study information to any potential patients for recruitment to this arm of the study. It is important patients are recruited in whom there is genuine and high clinical suspicion of luminal relapse rather than patients with low expectations of disease recurrence, for example those undergoing "routine follow up", or presenting with mild non- specific symptoms.

Although ileo-colonoscopy is the most robust standard of reference for colonic or terminal ileal disease recurrence, it is not always employed in suspected luminal relapse because of the morbidity of full bowel preparation and its invasive nature; reliance is placed on radiological imaging. In these cases, it would be unethical to expose patients to an invasive test purely for the purposes of the trial. In addition, restricting recruitment to patients undergoing ileo-colonoscopy as part of normal clinical care will likely produce spectrum bias; such patients are more likely to have known isolated colonic disease requiring endoscopic rather than radiological investigation.

Bearing these factors in mind, patients with suspected relapse requiring radiological investigation will be eligible if they have either objective measures of inflammatory activity, as described in detail below (raised CRP, calprotectin), and/or symptoms suggesting luminal stenosis (obstructive symptoms such as colicky abdominal pain, vomiting), and/or those with suspected relapse on endoscopy. This approach will also ensure that the incidence of relapse will be sufficiently high to match expectations in the power calculation (see section 6.7).

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 for their safety and 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

Patient inclusion criteria; new diagnosis

- Patients (≥ 16 years) undergoing or having undergone colonoscopy and either
    - newly diagnosed (within 3 months) 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
- Patient must have given written informed consent.

Patient inclusion criteria; suspected relapse-Closed to recruitment

- Patients ((≥ 16 years) with a known diagnosis of Crohn's disease with high clinical suspicion of luminal relapse indicating radiological investigation
    - High clinical suspicion defined as objective markers of inflammatory activity (raised CRP >8 OR raised calprotectin > 100), OR symptoms suggestive of luminal stenosis (including obstructive symptoms such as colicky abdominal pain, vomiting) OR abnormal endoscopy suggesting relapse.
- Patient must have given written informed consent.

6.3.1.3 Participant Exclusion Criteria

Exclusion criteria: All patients

- Any psychiatric or other disorder likely to impact on informed consent
- Evidence of severe or uncontrolled systemic disease, which at the PI's discretion renders the patient unsuitable for participation in the study.
- Pregnancy
- Contraindications to MRE (e.g. allergy to all suitable contrast agents, cardiac pacemaker, severe claustrophobia, inability to lie flat

Patient exclusion criteria; new diagnosis

- Final diagnosis other than Crohn's disease

- Patients undergoing surgical resection prior to colonoscopy

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

Radiologists performing US and MRE as part of the trial must have a declared interest in gastrointestinal radiology and experience of ≥20 of each procedure. All radiologists must hold the FRCR and if not consultant level must have undergone at least 12 months of sub-speciality gastrointestinal radiological training. Sonographers are eligible to perform USS providing they have undergone documented training in small bowel USS (either formal course or via their radiographer training program), perform small bowel USS in their usual clinical practice (with experience of ≥20 examinations) and are deemed competent the local trial lead Radiologist

6.3.1.5 Co-enrolment Guidance

Patients are eligible even if recruited into another trial e.g. for any therapeutic drug. Crohn's patients tend to be on a range of medication, so this approach would provide a true representation of standard care.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be recruited into the trial must be obtained from participants, after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as usual standard of care.

It is a requirement of the ethical approval that wherever possible the Patient Information Sheet (PIS) and Consent Form (CF) should be sent to pre-identified eligible patients with the invitation letter prior to their Out Patient Department (OPD) appointment by post or email. Consent may then be taken at this appointment if the potential participant confirms that they have had enough time to consider the matter.

In the case of those eligible patients who could not be pre-identified, they should be offered the PIS and CF at their OPD appointment. Following a discussion of the study and what it involves, those expressing an interest in participating should be invited to take the PIS and CF home with them for further consideration and an opportunity to discuss it with others. Verbal agreement should be obtained for further contact by telephone or email to confirm their interest and to make an OPD or Imaging Test appointment at which consent would be taken.

It may be pointed out to eligible patients who could not be pre-identified, but who have had as much time as they wish to consider the matter and who are content to do so, that they may exercise the option of providing consent at their initial OPD appointment.

Recruited patients may have undergone blood tests, biopsies, stool tests, small bowel imaging (including MRE and USS), questionnaires and colonoscopy and other clinical procedures prior to the date of informed consent as part of usual standard of care. Patients must consent to the results of such investigations to be accessible to the research team for retrospective use if this would help meet trial endpoints.

6.4 Comparators

This study is a non-randomised, observational study, comparing MRE and USS. All patients will undergo both imaging techniques for the purposes of this study. Recruited patients may already have undergone small bowel imaging, blood tests, colonoscopy etc. prior to recruitment.

All standard investigations undertaken as part of normal clinical care, either before or after recruitment, will be performed and initially interpreted by the usual radiologists, sonographers and clinicians employed at the recruitment site. Standard clinical reports will be produced and all investigations (and their results) will be freely available on hospital Picture Archiving and Communications System (PACS), Radiology Information System (RIS) and Clinical Data Repository (CDR) systems as per usual clinical practice.

A number of patients will also be selected to take part in a set of sub studies, as detailed in section 6.4.2.4.

6.4.1 Trial Imaging

6.4.1.1 MRE

Recruited patients will undergo MRE at their recruitment site. Magnetic Resonance Enteroclysis is not an acceptable alternative for MRE. The examination will be performed by the usual site radiographer team providing they are deemed competent by the site radiology lead.
The MRI platform (i.e. manufacturer and Tesla (T) strength) will be decided by the local radiologist according to scanner availability and their usual practice. It is anticipated most MREs will be performed at 1.5T. Exact imaging parameters will vary according to MRI platform but a minimum dataset of sequences will be acquired (full details given in appendix 1). The choice of oral contrast prior to MRE will also be according to the usual practice of the recruitment site.

A record will be kept of the nature of the oral contrast agent. Wherever possible a short proforma will be completed by the recruitment site, recording the volume of oral contrast ingested by the patient and over what time period the ingestion occurred before the MRE scan. In some patients MRE will have been performed as part of usual clinical care prior to recruitment and volumes of ingested oral contrast are unlikely to have been recorded. As long as the MRE has been acquired no more than 4 weeks prior to recruitment and according to the minimum dataset of sequences (appendix 1), the MRE will be eligible for inclusion in the trial and will not need to be repeated (see section 6.4.1.3 for protocol for appropriate blinding of radiologist interpreting the MRE if it is performed prior to recruitment).

6.4.1.2 Ultrasound

Recruited patients will also undergo small bowel USS at their recruitment site. This will be performed by a radiologist or sonographer fulfilling the criteria listed in section 6.3.1.4. For the purposes of the trial, patients will not receive any oral agent before the USS other than 2 cups of water to improve visualisation of the duodenum, which is optional. The USS platform (i.e. manufacturer) will be selected by the local radiologist/ sonographer according to scanner availability and usual practice. Exact imaging parameters will vary according to USS platform but a minimum probe frequency and examination technique will be required (full details given in appendix 3).

As described in section 8 (Sub Studies), a proportion of recruited patients will undergo hydrosonography in additional to standard USS. As long as the USS scan has been acquired no more than 4 weeks prior to recruitment and according to the minimum dataset of sequences (appendix 2), the USS scan will be eligible for inclusion in the trial and will not need to be repeated providing appropriate blinding of the performing radiologist/ sonographer can be assured as described in section 6.4.1.3. If full blinding as defined in 6.4.1.3 cannot be assured, the USS will be repeated.

6.4.1.3 Blinding of trial Imaging

Unbiased estimates of imaging test diagnostic accuracy can only be achieved if those interpreting the tests are unaware of the findings of contemporaneous imaging and endoscopy. For example a radiologist aware of endoscopically confirmed terminal ileal disease cannot give an unbiased evaluation of subsequent USS or MRE in the same patient. Similarly, interpretation of MRE or USS would likely be influenced by knowledge of the other test.

The standard NHS methodology for interpretation and storage of imaging test data is via the Picture Archiving and Communications System (PACS). These systems collate all the available imaging for a

particular patient into one place so it is openly and freely available for those interpreting new imaging data for the purposes of comparison. Each recruitment site will identify 2 participating radiologists (or 1 radiologist and 1 sonographer), so the MRE and USS for each recruited patient, can be conducted by an independent observer. Radiologists may interpret different modalities (MRE or USS) for different patients recruited to the trial over time, but for an individual patient must review just one of the modalities (MRE or USS) according to the blinding rule described below.

A. All trial imaging (i.e. MRE and USS) performed after recruitment

Each recruitment site can set up a system such that trial MREs can be interpreted in a blinded fashion away from previous imaging access to patient clinical information available on hospital computer data repository (CDR) systems. This can be achieved by interpreting imaging on standalone workstations remote from PACS. Alternatively if images are viewed on the hospital PACS systems, the patient identifiable data (i.e. patient id, prior imaging data and clinical history) must be removed / unavailable to maintain blinding of the radiologist.

Unlike MRE where interpretation occurs in isolation from the patient, USS interpretation occurs in "real time" during the actual examination by the performing radiologist/sonographer. It is therefore not appropriate for USS to be interpreted via a series of static images (or cine clips) stored on a workstation: this does not mirror how USS is used in clinical practice. To maintain blinding, the radiologist/sonographer performing USS must ensure they are equally isolated from all material usually freely available in the clinical setting (images, imaging and endoscopy reports etc.). Radiologists/sonographers performing USS after patient recruitment will complete the CRF documenting their findings away from the PACS and CDR systems. Wherever possible a research nurse will accompany the patient undergoing the USS to ensure the radiologist/sonographer completes the CRF without access to other clinical data or previous imaging. The patient and the radiologist/sonographer will be advised not to converse regarding diagnosis or findings

Clinical information made available to those reporting trial imaging

Radiologists/ sonographers will be made aware as to which arm of the study the patient has been recruited (i.e. new diagnosis or relapse). Such information would always be available to the radiologist/sonographers during usual clinical care and to withhold it would not reflect how the tests will be used in clinical practice. Furthermore, attempting to withhold this information may bias against MRE- radiologists/sonographers performing USS will almost certainly be unblinded during their verbal interaction with the patient. During the performance of the USS, the

radiologist/sonographer will not be permitted to interrogate the patient regarding current symptoms or past history. The only exception is that a radiologist/sonographer may clarify the nature of previous surgical procedures on the bowel as this will influence how they perform the USS and will be available to those reporting the MRE by the nature of the bowel anatomy. Patients will be instructed not to divulge clinical information to the radiologist/sonographer and a question will be included in the relevant section of the CRF, confirming that blinding was maintained during the scanning process.

B. Small bowel imaging performed before patient recruitment

The diagnosis of Crohn's disease is based on a combination of imaging, endoscopic, clinical, histological and biochemical findings. Patients who have a confirmed new diagnosis and are thus eligible for recruitment, will almost certainly have undergone small bowel imaging, interpreted by radiologists/sonographers unblinded to clinical, endoscopic and pathological data. In some instances this imaging will be MRE or USS. Reference should be made to the inclusion criteria (section 6.3.1.2).

(a) New diagnosis-Existing small bowel imaging performed using conventional tests (e.g. BaF, CT).

These patients will undergo both a study specific MRE and USS scan. Each recruitment site will allocate an individual radiologist to report the MRE, and another (or sonographer) to perform the USS. MRE and USS will be interpreted and stored as described in section 6.4.1.3 above.

(b) New diagnosis-Existing small bowel imaging performed using MRE or USS

In this scenario, the MRE or USS will very likely have been interpreted by a radiologist/sonographer unblinded to clinical data, including endoscopic findings as part of the usual standard of care. In the case of MREs conducted within 4 weeks of the patient signing the consent form, the images will be re-evaluated by another radiologist at the recruitment site (if blinding to previous imaging and clinical data can be ensured) on a workstation or PACS where the patient identifiable data is removed, and the CRF completed. If blinding cannot be ensured, the images will be reviewed by a radiologist from another recruitment site (after uploading onto 3D net, Biotronics Ltd (see section 6.9.3), allocated by the CCTU. This external radiologist will complete the CRF for the purposes of the trial.

If the existing imaging test is USS, due to the interactive nature of the test, static image review by an independent radiologist is inappropriate. The USS will therefore be repeated by a blinded radiologist

/sonographer from the recruitment site if the original performing radiologist/sonographer was unblinded to clinical information (other than suspected Crohn's disease) or findings of other tests. If the USS needs to be repeated, this should be done as soon as possible, and within three weeks of recruitment

c) Suspected relapse patients requiring small bowel imaging-closed to new recruitment

Patient recruitment can occur before trial small bowel imaging has been performed. Each recruitment site will allocate an individual radiologist to report MRE, and another (or sonographer) to perform the USS. MRE and USS will be interpreted and stored as described in section 6.9.3. Occasionally, a patient suspected of relapse may undergo MRE or USS as part of their normal clinical care before their eligibility for inclusion has been confirmed (e.g. awaiting a CRP level or calprotectin) and recruitment can occur. If the MRE has been performed within 4 weeks of recruitment and fulfils the minimum data set MRE protocol, the images may be used for the purposes of the trial and it does not need to be repeated. However, in this scenario, the MRE or USS will very likely have been interpreted by a radiologist/sonographer unblinded to clinical data, including endoscopic findings as part of the usual standard of care. In the case of MRE, the findings will be re-evaluated by another radiologist at the recruitment site (if blinding to previous imaging and clinical data can be ensured on a workstation or PACS where patient identifiable data is removed), and the CRF completed. If blinding cannot be ensured, the images will be reviewed by a radiologist from another recruitment site (after uploading onto 3D net, Biotronics Ltd (see imaging data storage section 6.9.3), allocated by the CCTU. This external radiologist will complete the CRF for the purposes of the trial. If the existing imaging test is an USS, due to the interactive nature of the test, static image review by an independent radiologist is inappropriate. The USS will therefore be repeated by a blinded radiologist/sonographer from the recruitment site. If the USS needs to be repeated, this should be done as soon as possible, and within 3 weeks of recruitment.

C. Reporting of trial imaging

A clinical report form (CRF) will be generated for MRE and USS in all recruited patients following the blinding protocols as previously described. The CRF will detail the technical quality of the examination, together with the presence, extent and activity of Crohn's disease. For the purposes of data recording, the bowel will be divided into duodenum, jejunum, ileum, terminal ileum and colon (rectum, sigmoid, descending colon, transverse, ascending and caecum). The jejunum will be defined as the proximal bowel lying largely to the left of a diagonal drawn from the right upper quadrant to the left lower quadrant demonstrating a typically feathery fold pattern. The terminal ileum or neo terminal ileum in the case of past resections will be defined as the last 10cm of small bowel upstream of the ileo-colonic junction. Contiguous disease involving the terminal ileum but

extending beyond 10cm will still be classified as terminal ileal disease (as opposed to both terminal ileal and ileal). Colonic segments will be defined using previously published definitions (Taylor SA 2003) .

For each segment, radiologists/sonographer will indicate the presence or absence of Crohn's disease together with their diagnostic confidence from 1 to 6 (low to high). Data on the length of disease, activity, the presence of functionally significant stenosis, and extra-enteric complications such as abscess or fistulae will also be recorded. Standard definitions will be used for the identification of Crohn's disease (Tolan DJ 2010); (Maconi G 2006). All distinct sections of disease in a segment will be recorded on the CRF. Distinct sections of disease within a particular segment will be defined as non-contiguous if 3cm or more of normal appearing small bowel is present between disease sites. Disease sections separated by less than 3cm of normal bowel will be considered a single disease section (contiguous) for the purposes of data recording.

Disease activity on MRE will be assessed using published validated criteria (Tolan DJ 2010), notably mural thickness, mural and peri-mural T2 signal, post-contrast enhancement pattern and level, and presence of ulceration (appendix 3). Disease activity on USS will be assessed using published criteria regarding wall thickness and increased mural Doppler signal (Tolan DJ 2010) but will also consider mucosal and submucosal thickness and definition, as well as the appearance of the extra-enteric fat (appendix 3). Reporting radiologists will state if, in their opinion and based on these criteria, any disease present is active or non-active on a segmental and per patient basis.

Reporting radiologists will also record if the T1 weighted contrast-enhanced sequences and the diffusion sequences aided their diagnosis over and above review of conventional True FISP and T2 weighted sequences and if so why (change of diagnosis/ disease presence and/or activity; change in diagnostic confidence without change in overall diagnosis).

Once the CRF has been completed and signed, the radiologist/sonographer will provide a full clinical report as per usual clinical practice for release to the clinical team using the usual hospital PACS and radiological information (RIS) systems. Because this final clinical report may be used by the clinicians for direct patient management, radiologists/sonographers may now be unblinded to full clinical data as per their standard clinical practice.

D. Handling of MRE and USS reports

The clinical reports of the MRE and USS will be made fully available to clinical teams who will be at liberty to act upon them as per usual clinical practice. Any additional tests generated by the MRE and USS will be recorded on CRFs, and their results available to the consensus reference panel (section 6.4.4)

For the purposes of the trial, if MRE and USS are discrepant for the presence of disease in the absence of a third arbiter test, an additional test will be performed as detailed in the next section.

E. Generation of additional imaging for discrepant MRE and US

There is no single reference standard for the proximal small bowel upstream of the terminal ileum (which is usually assessed as part of ileo-colonoscopy). There is a clear risk of incorporation bias if MRE and USS alone form the standard of reference for the presence or absence of disease in the proximal bowel. Many recruited patients will also undergo conventional small bowel imaging as part of usual clinical care, notably BaF, CT enterography and in some cases capsule endoscopy. The results of these tests will provide at least one independent small bowel imaging test for the consensus reference standard for the proximal small bowel, or non-endoscopically visualised terminal ileum (see section 6.4.4).

For those recruited patients whose <u>only</u> small bowel imaging is MRE and USS, a third test will be performed if these tests are discrepant for the <u>presence</u> of small bowel disease
Discrepancy will be defined as

a) The presence of disease in the terminal ileum or neo-terminal ileum (last 10cm of small bowel) reported on only MRE or USS in the absence of visualisation of the terminal ileum at endoscopy
b) The presence of disease in the small bowel upstream of the terminal ileum (last 10cm of small bowel) reported on only MRE or US. Discrepancy will also be deemed to have occurred if one test (either MRE or USS) reports more discrete sites of disease than the other (a discrete site of disease is defined as a section of disease separated by 3cm or more of normal bowel from other disease sites). For example if both MRE and USS record ileal disease but only USS reports jejunal disease, they will be judged as discrepant.

For the purpose of generating additional tests, discrepancy will not be judged present if MRE and USS agree on disease presence but are discrepant for the length of disease, activity of disease or extra-enteric complications. If MRE and USS are concordant for the presence of

isolated proximal small bowel disease but differ in segmental location (e.g. ileum versus jejunum), the recruitment site clinical and radiological teams will review the imaging and opine if the tests are in fact likely concordant (i.e. the same abnormality has been detected) or likely discordant i.e. true disagreement about the presence of absence of disease in a segment, in which case a third arbiter small bowel imaging test would be indicated as described below.

If USS and MRE are discrepant for the presence of small bowel disease according to the definitions above, the clinical team at the recruitment site in consultation with site radiologist will perform a third arbiter small bowel examination. The choice of this examination will be at the discretion of the recruitment site and may include barium fluoroscopy, CT enterography, MRE enteroclysis, conventional endoscopy, or capsule endoscopy. Emphasis should be placed by sites on performing a new modality (other than MRE or USS) as the third test, but a repeat "trouble shooting" MRE or USS are permitted if an alternative modality is thought inappropriate by the clinical team or patient. Wherever possible, the third arbiter test should be performed within 8 weeks of MRE or USS (whichever is performed last).

The recruitment site clinical team will also be free to perform an arbiter small bowel imaging test if they suspect the disease phenotype differs from that reported on the MRE and USS.

A full unblinded report of the generated test will be provided as per usual clinical practice and be made available at the consensus reference standard meeting (see section 6.4.4 below).

6.4.2 Assessments

6.4.2.1 Disease activity

Patients undergoing colonoscopy as part of usual clinical practice will often have a photograph of the terminal ileum taken by the endoscopist, as well as biopsies of the colonic and small bowel mucosa. Recruited patients will give consent for the photograph and biopsies (if taken) to be used by the trial team to assign their disease status and activity (see reference standard below). As part of the standard reference for disease activity, recruited patients will complete a Harvey Bradshaw index-HBI (appendix 4). Calculation of this index requires examination by a suitably qualified staff member who will be designated by the recruitment site. The serum CRP level will also be measured along with the faecal calprotectin. Completion of the HBI and collection of the CRP and calprotectin should be within 3 weeks of either the MRE or USS (unless both imaging examinations were performed over 3 weeks prior to recruitment as part of clinical practice, in which case the test will be

collected as soon as possible after recruitment). As noted in section 6.3.1.6, patients will consent to use of clinical data acquired as part of routine care prior to the date of written consent. If serum CRP, faecal calprotectin or HBI have been collected as part of clinical care prior to the date of consent, these do not need to be repeated if the date of collection is within 3 weeks of either the MRE or USS used for the trial. The HBI, CRP and calprotectin will be repeated 3 months post-baseline in order to help evaluate the success of any therapeutic intervention which will be used to inform the reference standard (section 6.4.4). Although repetition at 3 months is desirable, it is recognised this time point may not always be convenient for patients, and a date range of collection between 10 and 20 weeks after the date of the initial samples is acceptable. Patients not wishing to provide an initial and/or repeat blood or stool sample for analysis of CRP or calprotectin may consent to participate in the imaging requirements of the trial (MRE and USS) and HBI only and remain eligible.

6.4.2.2 Cost Effectiveness

Resource use data for the main drivers of hospital costs will be collected using a study specific CRF. Additionally, patient resource use diaries will be administered to all patients at consent and then once more at 3 months. The diaries will be used to collect data on primary and community care contacts for the 6 month period of follow up from recruitment. The initial diary and questionnaire will be given to patients upon consent as part of their registration pack. Subsequently, diaries and questionnaires will be posted to patients by trial sites or handed to them (for example when the patient returns for the 3 month repeated calprotectin and HBI-see above). Each patient will also be asked to complete an EQ-5D-5L questionnaire (Euroqol) at consent and at 3 and 6 months.

6.4.2.3 Psychology questionnaires

Patients recruited before MR enterography has been performed will be provided with a questionnaire pertaining to their experience of the MRE during the test and their recovery for a period of 2 days afterwards. The questionnaire will be given to the patient at consent. Copies will be kept in the MRI scanner facilities of the recruitment site should they be required. The questionnaire will be half completed on the day of the scan, without input from study staff, with the second half being completed 2 days later. Patients will thus take the questionnaire home with them and will be provided with a stamped address envelope for return to the trial team at UCLH. The research nurse at site or the centrally based research fellow will remind each patient to complete the questionnaire.

Patients will be asked to leave the first part of the questionnaire (completed on the day of their scan) at the recruitment site and take the second part home.

A second questionnaire will be given to all recruited patients to ascertain their experience of all imaging tests undergone during their diagnostic episode. The focus will be on their experience of MRE and USS, but data will be collected on their overall mood, as well as the attributes they feel are most important about diagnostic tests. The questionnaire will be included in the registration pack given to the patient at consent together with a stamped addressed envelope for return. Patients will be instructed to return the questionnaire after they have completed all their imaging tests and research nurses and research fellow will remind patients to complete the questionnaires at the appropriate time. The timing of completion for this questionnaire will be variable depending on the small bowel tests patients undergo, but will usually be within 4-6 weeks of recruitment.

6.4.2.4 Sub Studies

A. Diagnostic benefit of oral contrast administration prior to USS ("hydrosonography")
Recruitment sites will be invited to opt into a sub study of hydrosonography. A sample of 75 recruited patients will undergo unprepared USS, as per study protocol, but in addition undergo hydrosonography following an oral contrast load. The same radiologist/sonographer will perform both examinations to limit the potential for inter-observer variation. The standard USS CRFs will be completed pertaining to disease presence, location, extent and activity, with diagnostic confidence after each individual examination i.e. without and with oral contrast. The results of both examinations will be compared against the final consensus reference standard, and the additional diagnostic benefit (if any) of an oral contrast load assessed.

Additional consent for participation in the hydrosonography sub study will be obtained from recruited patients. Because of the potential side effects of an oral contrast agent (such as diarrhoea), it is permissible for patients to undergo hydrosonography immediately after their MRI, making use of the oral contrast given for the MRI.
Wherever possible however, preference will be given to performing USS before and after an oral contrast load additional to that used for MRI. In this scenario, patients will ingest up to 1L of oral contrast according to recruitment site preference and usual practice over 50-60 minutes prior to the USS. The findings on the standard USS will be used for the purpose of the main trial and primary endpoints.

B. **Inter-observer variation in USS interpretation**

Ideally, a sample of at least 5 patients at each recruitment site will undergo two USS examinations by two independent radiologists/sonographers (adhering to the blinding protocols required by the main trial) to define rates of interobserver variation. The report produced by the first reader will be used for the purposes of the main trial; the second review will provide data only for this sub study. The USS CRF pertaining to disease extent, location and activity will be completed by both radiologists/ sonographers independently. The two USS examinations should ideally be performed on the same day, although a period of 2 weeks between the examinations will be permissible. Additional consent for participation in the sub study will be obtained from recruited patients. Patients may be recruited for both the hydrosonography trials and the study of inter-observer variation.

C. **Influence of oral contrast agent and ingested volume on small bowel distension during MRI**

Recruitment sites use different oral contrast agents and this will be permitted in the trial. As noted above the nature of the oral contrast will be recorded for all recruited patients and wherever possible the volume ingested prior to the MRI will also be recorded. MRI datasets will be collected centrally (see section 6.4.1) allowing retrospective study. A research fellow will grade the quality of small bowel and colonic distension for all datasets devising a grading system after review of the available literature. The quality of distension will them be compared across different oral contrast agents and ingested volume. The patient reported symptoms in the administered questionnaires will also be correlated with distension quality and type of oral contrast agent

D. **Contribution of contrast enhanced and diffusion weighted imaging to MRI evaluation**

As noted in section 6.4.1, reporting radiologists will prospectively note on the MRI CRF the benefit, if any, of contrast enhanced and diffusion weighted images over conventional T2 weighted images.
A retrospective reader study using the centrally collected anonymised MRI datasets will be performed. Participating radiologists (up to 15) will review the MRI datasets using a locked sequential viewing paradigm. Using the MRI CRF, radiologists will analyse the MRI datasets using just T2 weighed and TruFISP sequences. They will then review the diffusion weighted images, re-completing the CRF before finally reviewing the contrast enhanced sequences and completing the final 3rd CRF. Reporting times for each sequence block will also be recorded. The influence of diffusion weighted and contrast enhanced images on radiologist diagnostic accuracy (compared to the consensus reference and diagnostic confidence) will be assessed.

E. Inter-observer variation in MRI interpretation

Each radiologist (n=12) will read a sample of 20 studies acquired and interpreted at a different site in order to define rates of inter-observer variation. MR examinations will be uploaded to the central image server used for image storage during the trial (3D net), which will facilitate these interpretations, which take part over the course of the study. Radiologists will read scans acquired at other recruitment sites to reduce recall bias for their own patients. Proformas detailing disease extent, location and activity will be completed.

F. **Influence of radiologist diagnostic confidence on MRI and USS accuracy**

Interpretation confidence (scored 1-6 by reporting radiologists/sonographers) scores will be related to diagnostic accuracy.

6.4.3 Patient follow up

Patients will be followed for 6 months to provide clinical outcome data, allow for repeat of HBI, CRP and calprotectin at 3 months (see section 2.2: Table of Assessments), populate cost effectiveness models, and to collate data contributing to the ultimate reference standard.

Data collation will be coordinated by UCL CCTU. Follow-up data will be recorded on study-specific CRFs which detail imaging investigations, endoscopy, surgical interventions, major medication changes, outpatient visits and inpatient stays during the time period. If patients undergo surgery, a CRF will be completed detailing the extent, activity and complications of disease found at surgery which will be available during the consensus reference standard review. During this follow up period, patients will complete 2 resource use diaries (one for month 1-3 and one for months 4-6) and the EQ 5D at recruitment, 3 and 6 months.

6.4.4 Reference standard

There is no single reference standard that can be uniformly employed for the staging of Crohn's disease. Diagnosis and staging in clinical practice is made on a combination of clinical, endoscopic, imaging, histopathological and biochemical criteria. The HTA has given guidance regarding the evaluation of diagnostic tests when there is no "gold standard"(Rutjes AW 2007). The current trial will utilise the construct reference standard paradigm (panel diagnosis) incorporating the concept of clinical test validation i.e. whether the results of an index test are meaningful in practice. Specifically patients' clinical course will be followed for 6 months after recruitment during which time the findings of the MRE and USS will have been acted on by clinicians and incorporated into their therapeutic decision making. Ileo-colonoscopy (combined with histological assessment of tissue biopsies) is considered the most robust standard of reference for diagnosis and staging of Crohn's disease within the colon and terminal ileum (last few centimetres of small bowel). All newly diagnosed patients will have undergone ileo-colonoscopy as part of their normal clinical care.

Each recruitment site will convene a consensus panel, the availability of which will be determined during the site selection process, to derive the reference standard for disease presence, extent and activity at the time of the trial imaging in those patients recruited to date. The panels will consider all available clinical information including the results of conventional investigations, endoscopy

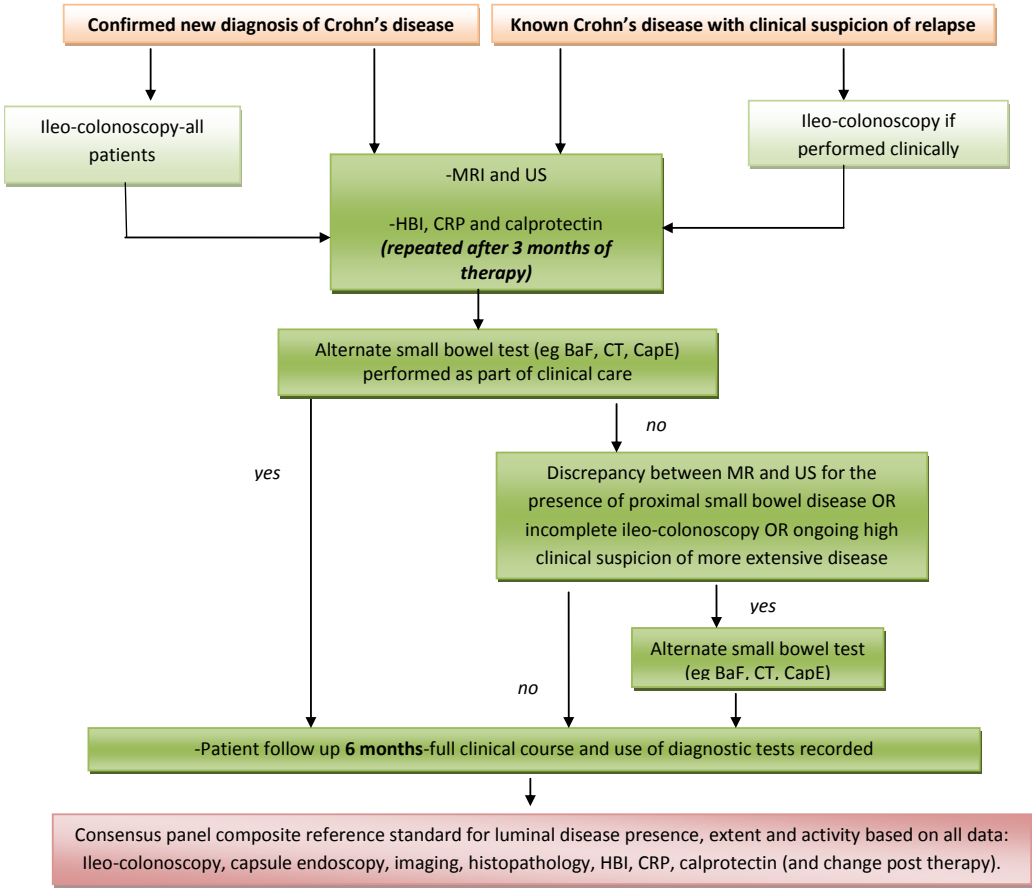
(conventional and capsule), MRE, USS, surgical findings**,** histopathology (surgical resection and biopsies), HBI, CRP, calprotectin (and changes thereof in response to therapy), follow up imaging and clinical course. The UCL CCTU will coordinate collation of these data via submitted CRFs over the preceding 6 months for presentation to the panel. Each site will host consensus panels to consider patients recruited at that site. All imaging studies will be available for review on local PACS systems if required.

Each panel will consist of at least one (and ideally two) gastroenterologists and 2 radiologists (1 local to the site and 1 external). A member of the central trial team will attend each consensus meeting to ensure similar criteria are used in defining disease extent. A histopathologist should be available to the panel if required. Each panel will complete the final reference standard CRF against which the diagnostic accuracy of imaging tests will be compared.

The presence or absence of disease per bowel segment will be decided by the panel based on all available information as listed above. The panel will decide if the patient had active disease at the time of trial imaging. Patients with active disease should have objective evidence with at least one of the following: (i) ulceration as seen at endoscopy (ii) measured CRP >8 mg/l (iii) measured calprotectin >250 (iv) histopathological evidence of acute inflammation based on biopsy or surgery within 2 months of trial imaging.

In addition the presence of active disease in the terminal ileum will be assigned based on the presence of ulceration on the endoscopic photograph (if available) and histological analysis of biopsies by the site histopathologist using a simplified activity score (appendix 5). All available terminal ileum biopsy samples will be scored by the recruitment site histopathologist using the Histological Activity Index (HAI). Whenever possible depending on local histopathological resource, the more detailed Comprehensive Activity Index will also be scored. Data in agreement between panel members with the final reference standard will be collected by CRF.

Reference standard summary



HBI-Harvey Bradshaw Index. CRP= C reactive protein, MRI=magnetic resonance imaging. US-ultrasound, CapE=capsule endoscopy, BaF-barium fluoroscopy, CT=computed tomography

6.4.5 Modelling of therapeutic impact

An assessment of the impact of MRE and USS on diagnostic confidence and patient management compared to conventional imaging will be made in retrospect at each recruitment site. Each site will attempt to complete the process for 20 patients, although may do more if they have sufficient resources. Priority will be given to patients in whom the findings of MRE, USS and / or clinical testing are discrepant.

As already discussed with potential sites, each site will identify at least one site specific gastroenterologist aided if required by a radiologist or research team member, who will conduct an exercise with regard to diagnostic and therapeutic impact. During this process the gastroenterologist will review the clinical data (symptoms, clinical examination findings, biochemistry and endoscopy data) using standard clinic data based on the data already collected on study CRFs. This summary will be provided initially by the UCLH research fellow and then by the CCTU on paper or by electronic proforma. . To minimise the risk of recall bias by the

gastroenterologist recognising the patient based on the clinical data, some of the exercise will be undertaken by sites reviewing data collected at other recruitment sites. All data transferred between sites will be pseudoanonymised with only the patient study ID and no personal data. The gastroenterologists will record their diagnostic confidence for the presence and location of Crohn's disease, its activity, extra-enteric complications, need for additional investigations and planned therapeutic strategy based on a previously published proforma (Hafeez R 2011). The gastroenterologist will then be presented with the findings of one of the imaging modalities (MRE, USS or conventional imaging such as CT, BaF (if performed)), and will re-complete the proforma in light of these imaging findings, noting changes (if any) in their diagnosis, diagnostic confidence or therapeutic decision. After a minimum of 2 weeks, the process will be repeated, although another imaging modality will be presented to the gastroenterologist. Data will be randomised in the order of revelation of the imaging modalities for each individual patient so the order of revelation is defined upfront. The patient will be reviewed a third time if they have all 3 imaging modalities (conventional, MRE and USS) available using the same process. After all 3 modalities have been revealed, the gastroenterologists will indicate their final diagnostic confidence and therapeutic impact on the proforma considering all available clinical and imaging information. For convenience it is likely sites will group a number of patients to be reviewed at one time. The same gastroenterologist will complete all diagnostic and therapeutic impact proformas for a particular patient. Clinical Data will be collected on recall bias as part of this process using CRFS.

6.4.6 Central collection of trial imaging data

Recruitment sites will send fully anonymised MRE and USS datasets on CD identified by study number only (compliant with local data protection rules) to the CI at University College London Hospital where they will be stored in a secure lockable office. Images will be uploaded onto 3D Net, a cloud based PACS viewing software hosted by Biotronics 3D for image storage and used in future sub studies, as discussed in section 6.4.2.4.

6.4.7 Trial Imaging QA

MRE datasets from recruited patients will be reviewed at UCLH for image quality (appendix 6). The radiologist performing USS will provide a cine clip (or static image if cine clip not possible) of the ileo caecal valve as a marker of technical adequacy of the examination which will be reviewed centrally at UCLH.

6.4.8 Histology QA

Each site will send a sample of 5 terminal ileal biopsy slides with their histological scores during the first year of the trial to the central histopathologist at UCLH using established standard NHS procedures for transport of pathological slides. The histopathologist will review the scores assigned and feed back to the local histopathologist any major discrepancies. A further 5 slides will be sent following the same process across years 2 and 3 (i.e. each site supplies 10 terminal ileal biopsy slides in total).

6.4.9 Protocol Treatment Discontinuation

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

- An adverse event which precludes preceding with trial interventions, hence preventing the generation of MRE/USS data
- Inability to complete trial intervention e.g. MRE, which is realised post consent
- Inter-current illness that prevents completion of trial
- 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 trial is entirely voluntary, the participant may choose to discontinue trial interventions at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing the trial, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol interventions, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis only if they have undergone both MRE and USS. They otherwise will be replaced.

6.5 Outcomes

6.5.1 Primary Outcomes

Difference in sensitivity per patient, of MRE and USS, as diagnostic tests for the correct identification and localisation of small bowel Crohn's disease.

- Ability to detect presence of disease (both active and inactive disease)

- Sensitivity for each test is measured against a reference standard by consensus panel review at or after 6 months. Reference standard includes tests as available from clinical pathway including: ileo-colonoscopy, capsule endoscopy, imaging, histopathology, HBI, CRP, calprotectin including post therapy follow up.

Subgroup analysis for separate population of new versus relapse patients

6.5.2 Secondary Outcomes

1. Difference in specificity of MRE and USS for correct identification and localisation of small bowel Crohn's disease per patient.
   - Additional analyses will include extension to include both small bowel and colonic Crohn's disease for per patient analysis of (i) the difference in sensitivity and (ii) difference in specificity
   - Subgroup analysis for separate populations of new versus relapse patients
2. Comparison of USS and MRE to detect patients with active small bowel Crohn's disease

   (i) Difference in sensitivity and specificity per patient

   (ii) Difference in sensitivity and specificity of terminal ileum segment in subgroup of patients based on colonoscopic reference

   (iii) Additional analysis in colonic Crohn's for patients with colonoscopic reference for (a) Difference in sensitivity and specificity per patient (b) Difference in sensitivity and specificity of colonic segments
   - Subgroup analysis for separate populations of new versus relapse patients
3. Comparison of USS and MRE diagnostic accuracy to detect presence of disease (either active or inactive

   (iv) Difference in sensitivity and specificity per patient in small bowel and colonic Crohn's disease

   (v) Difference in sensitivity and specificity of terminal ileum segment in subgroup of patients undergoing colonoscopy in small bowel and colonic Crohn's disease

   (vi) Difference in sensitivity and specificity per segment in subgroup of patients undergoing colonoscopy in colonic Crohn's
   - Subgroup analysis of (i) and (ii) in patients with small bowel only
   - Subgroup analysis for separate populations of new versus relapse patients
4. Comparative impact of MRE and USS on clinician diagnostic confidence for the presence of Crohn's disease and influence on patient management, to each other and to conventional imaging

- Subgroup analysis for separate populations of new versus relapse patients

5 The lifetime incremental cost and cost-effectiveness of assessment using MRE and USS compared to each other, and to conventional imaging.

6 Diagnostic accuracy and radiologist confidence using hydrosonopgraphy compared to conventional USS

7 Comparative patient experience of MR and USS

8 Diagnostic impact of novel MRE sequences, notably diffusion weight imaging on disease detection, diagnostic confidence and disease activity assessment

9 Inter-observer variation in the evaluation of MRE and USS datasets by radiologists, and to assess the impact of diagnostic confidence on accuracy

6.6 Participant Timeline

After consent patients will undergo MRE and USS (if not already performed as part of clinical care), provide a stool sample for calprotectin measurement, blood tests for CRP measurement and complete a symptom diary and clinical examination for calculation of the HBI. An EQ5D-5L questionnaire will also be completed, and patients will begin to complete a patient resource diary for months 1-3.

At 3 months (range 10-20 weeks) post recruitment, patients provide a stool sample for calprotectin measurement, blood tests for CRP measurement and complete a symptom diary and clinical examination for calculation of the HBI. Wherever possible this will be done to coincide with a routine patient hospital visit. The patient will begin to complete a patient resource diary for months 4-6.

At 3 and 6 months the patient completes an EQ5D-5L questionnaire.

6.6.1 Early Stopping of Follow-up

If a participant who has undergone both MRE and USS chooses to discontinue their trial involvement, 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 trial, even though they will no longer undergo the trial interventions. 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 trial. UCL CCTU should be informed of the withdrawal in writing using the appropriate METRIC trial 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.

Participants who stop trial follow-up early will be replaced if they have not undergone both MRE and USS.

6.6.2 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 trial 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.

6.6.3 Loss to Follow-up

Patients will be replaced if they are irretrievably lost to follow up such that insufficient follow up clinical data is available to inform the 6 month reference standard

6.6.4 Trial Closure

For regulatory purposes the end of the trial will be after the final at or after 6 months consensus meeting following recruitment and 6 months follow up of the final patient at which point the 'declaration of end of trial' form will be submitted to ethical committees, as required.

6.7 Sample Size

Power is based on the primary outcome stipulated by the HTA-diagnostic accuracy for Crohn's disease extent. In this section, MRI will be used as the basis of statistical sample size for MRE.

There are two aspects to correctly assigning disease extent-correctly detecting the presence of disease AND correctly assigning its segmental location. For example a test which correctly identifies disease in the terminal ileum of the small bowel, but misses disease in the proximal bowel (e.g. jejunum) will likely result in an incorrect patient management decision i.e. such a test would be inaccurate for defining the extent of Crohn's disease. Power is thus based on a two facetted compound accuracy measure (disease presence and disease location).

Patients with disease identified by reference test

Primary outcome: Test accurate for disease extent	Correct identification of disease presence	Test accurate for disease extent?
Y	Yes –disease identified	Yes-all segments identified
N	Yes –disease identified	No- one or more segments missed
N	Yes –disease identified	No- incorrect segment(s) identified
N	N- no disease identified	No disease identified

Power calculation

Comparison of MRI to USS accuracy - both against a composite reference standard

- Study powered to show difference in sensitivity for disease extent (compound of disease presence and correct disease location). Assume moderate correlation between the tests as both are imaging tests:
- Paired study design - all tests on all patients
- 90% power type II error, type I error 5% ($p<0.05$)
- Per patient unit of analysis
- Combined patient population (i) new patients diagnosed with Crohn's (ii) patients with suspected relapse. Both groups have approximately 70% prevalence of small bowel disease

Assumptions

- Sensitivity for correct disease presence (see assumption 1 below)

  MRI 93%

  USS 88%

- Sensitivity for correct disease location (see assumption 2 below)

  MRI 90%

  USS 83% (encompassing 30% sensitivity for the 5-10% of patients with proximal small bowel disease)

- Compound accuracy measure (disease presence and disease location)

  10% difference in sensitivity between tests

  MRI **83%** = 93% (disease presence) x 90% (disease location)

  USS **73%** = 88% (disease presence) x 83% (disease location)

  68% test results are positive with both USS and MRI. Reasonable correlation assumed as both tests are imaging tests. A higher correlation would result in a lower sample size.

- Prevalence of small bowel Crohn's disease -**70%** (new diagnosis and relapsing patients). See assumption 3 below.

Sample size calculation

- Sample size method (Alonzo TA 2002)

Power beta	Alpha	Sens MRI	Sens USS	% Patients USS+MRI+	% Discrepant cells	Total DP	Prevalence	Total N	Total with 10% LFU*
90%	0.05	0.83	0.73	0.68	0.2	210	0.7	301	334
80%	0.05	0.83	0.73	0.68	0.2	157	0.7	224	249

* LFU loss to follow up

Total cohort=301 (210 patients with disease)

Allowing 10% loss to follow up, **total cohort=334** (167 new diagnosis patients and 167 relapse patients)

Evidence base for underlying assumptions of test diagnostic accuracy

Assumption 1: Estimates for sensitivity of disease detection with USS and MRI

Summary sensitivity for detection of small bowel disease:

MRI-93%, USS-88% (figure 1)

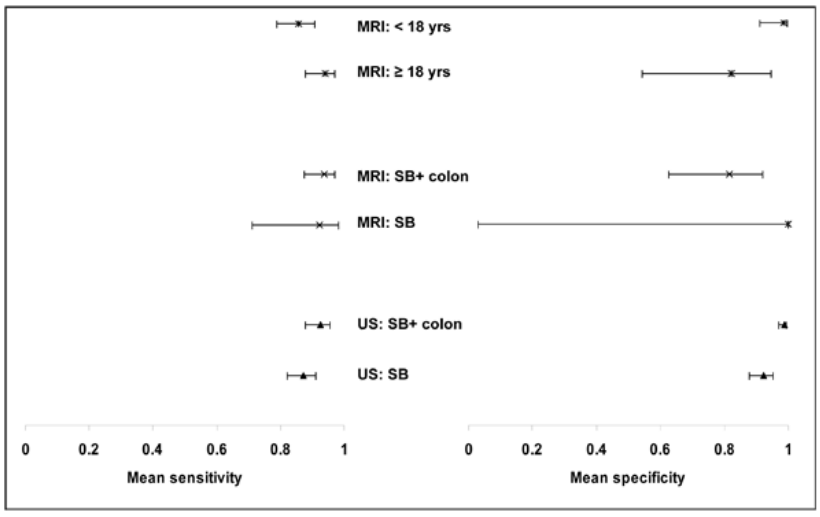


Figure 1 (Horsthuis K 2008)

Assumption 2: Disease location

The trial team have contacted the authors of this systematic review and there is insufficient data to look at the differential sensitivity of imaging tests for proximal and distal small bowel disease.

Diagnostic accuracy for proximal small bowel disease (Fraquelli M 2005)

Disease Prevalence assumptions (Baumgart DC 2007)

Assumption 3: Disease presence

Highest level of evidence is a systematic review by (Horsthuis K 2008)

author	imaging	n	Disease prevalence
Ochsenkuhn	MRI	25	0.72
Shoenut	MRI	20	1.00
Koh	MRI	30	0.77
Miao	MRI	30	0.77
Rieber	MRI	48	0.56
Laghi	MRI	75	0.59
Darbari	MRI	58	0.78
Solvig	USS	59	0.34
Miao	USS	30	0.77
Calabrese	USS	28	0.89
Andreoli	USS	41	0.78
Sheridan	USS	127	0.32
Tarjan	USS	73	0.59
Rispo	USS	80	0.63
Limberg and Osswald	USS	440	0.18
Reimund	USS	118	0.74

Study power-Secondary outcomes

Disease activity

Methods

Crohn's disease activity will be considered on a per segment (for the terminal ileum) and per patient basis.

Comparison of MRI to USS accuracy - both against a composite reference standard

- Study powered to show a difference in sensitivity for activity. Assume moderate correlation between imaging tests.
- Paired study design - all tests on all patients
- 80% power type II error, type I error 5% ($p<0.05$)
- Combined Patient population (i) new patients diagnosed with Crohn's (ii) patients with suspected relapse. Both groups have approximately 70% prevalence of small bowel disease
- Sample size method (Alonzo TA 2002)

Per segment (terminal ileum)

Segmental assessment of disease activity can only be meaningfully acquired using an endoscopic reference (global markers such as HBI, calprotectin are not segment specific). The terminal ileum is the most robust segment to acquire endoscopic assessment of disease activity given its ease of identification and fundamental importance in the diagnosis and assessment of Crohn's disease. Endoscopic evaluation of the terminal ileum will be available in around 200 patients (all new diagnosis and one third of relapse). The HTA requirement to study those with a new diagnosis of Crohn's disease means prospective collection of CDEIS will not be possible i.e. endoscopy will in the main be performed before recruitment and CDEIS is not recorded as part of routine clinical practice). Activity in the terminal ileum will thus be assigned by the consensus reference panel based on the endoscopic report, endoscopic images (photographic documentation of the terminal ileal appearances is routine at recruitment sites), and histology of TI biopsies, also routine.

Assumptions

- Sensitivity for correct presence of active disease (see assumption 4,5 below)

  MRI 75%

  USS 60%
- 50% test results are positive with both USS and MRI. Reasonable correlation assumed as both tests are imaging tests. A higher correlation would result in a lower sample size.
- Prevalence of small bowel Crohn's disease is **70%** (new diagnosis and relapsing patients). See assumption 3 above.
- One segment per patient: terminal ileum

Power	Type I error	Sens MRI	Sens USS	% Patients USS+MRI+	% Discrepant	total DP	prevalence	Total N	Total with 10%

					cells				LFU
80%	0.05	0.75	0.60	0.50	0.35	122	0.7	175	195

Sample size calculation

Sample size method (Alonzo TA 2002)

Total N=122 disease positive segments at one per patient. This corresponds to 175 patients at 70% per patient prevalence and 80% power. **195 patients** will be required allowing 10% loss to follow up.

Endoscopic evaluation of the terminal ileum will be available in around 200 patients (all new diagnosis (n=167) and one third of relapse (n=55; 0.33x167).

Per patient

- Sensitivity MRI 88% (see assumption 6)
- with cohort powered for primary outcome, we have 80% power to detect a 10% change in activity per patient.

Power	Alpha	Sens MRI	Sens USS	% Patients USS+MRI+	% Discrepant cells	total DP	prevalence	Total N	Total with 10% LFU
80%	0.05	0.88	0.78	0.70	0.26	204	0.7	292	324

Evidence base for underlying assumptions of test classification of disease activity:

Assumption 4: Classification of activity per segment

Two systematic reviews include meta-analyses of MRI in the classification of Crohn's disease activity (Panés J 2011) (Horsthuis K 2009).

The largest study directly comparing USS with MRI in the same patients include 30 patients, 23 with disease (Miao 2002).

Assumption 5: Per segment sensitivity for correct disease activity classification (encompassing prevalence estimates) (Panés J 2011).

MRI-**78%**

USS-**60%**

I.e. an **18%** difference between tests

Assumption 6: Per patient sensitivity for disease activity

(Panés J 2011)An assumption of 88% sensitivity for MRI is based on 6 studies with a total of 118 DP patients (range 7 to 28 per study). Although the Panes SR identifies a range of sensitivity for USS of 77-100% with a summary of 85% sensitivity this is based on 5 studies with between 23 and 47 patients with active disease per study. However these results are likely to be over optimistic due to several sources of bias

(1) threshold effects: sensitivity is quoted for two threshold values for bowel wall thickness, >2.5mm for ileal segments >3.0mm for all segments, with sensitivity of **75% and 48%** respectively. If thresholds are chosen to optimise diagnostic performance within a study, sensitivity values are over-estimated.

(2) disease spectrum bias: sensitivity varies from **33% to 67%** depending on the segment with active disease and a threshold of >3.0mm. In addition the sensitivity varies with disease severity (mild, moderate, severe).

- Studies with very small numbers of patients will have high potential for disease spectrum bias.

a. Patient management

- Revelation of MRI or USS result first to the treating gastroenterologist will be randomised
- Patient management form 1:Gastroenterologist will complete a patient management form based on first test revealed (MRI or USS) alongside standard clinical information
- Patient management form 2: Gastroenterologist will complete a second patient management form based on second test revealed (MRI or USS) alongside standard clinical information.
- Patient management form 3. Gastroenterologist will complete a final patient management form which reflects their final management decisions based on all available test data. This will become the standard of reference for patient management.
- Power based on comparison between individual test-based management decision (MRI or USS) and the final management plan.

<u>Methods</u>

- Comparison MRI first test revealed compared to USS first test; both compared to reference standard.

- Unpaired index tests
- Power based on agreement with patient management by reference standard (surgery vs. change in medication vs. other)

Assumptions

- Based on local audit of MRI practice, assume 95% agreement between management decision based on MRI and the final management decision
- 70% prevalence of disease
- 210 patients with disease, 105 per arm (i.e. MRI or USS revealed first) . Based on 334 patients in study cohort (based on primary outcome), allowing for 10% loss to follow up and 70% prevalence.

A sample size of **105 patients with disease in each arm** (i.e. MRI or USS revealed first) gives 80% power to detect a **13% difference in patient management** between MRI (95% agreement to reference) and USS (83% agreement to reference).

b. Difference in diagnostic accuracy between MRI and USS in each patient cohort (new diagnosis and relapse)

Methods: as primary outcome

156 patients (allowing for 10% loss to follow up) gives 80% power to detect a **13%** difference in sensitivity between MRI and USS for both recruited cohorts separately (i.e. less than the required 167 per cohort for the primary outcome)

- Sample size method (Alonzo TA 2002)
  Assume same % agreement between tests as primary outcome, same 83% sensitivity for MRI.
- 80% power to detect 13% difference in sensitivity based on primary outcome for each patient group (new or recurring).

Power	Alpha	Sens MRI	Sens USS	% USS+ & MRI+	% discrepant cells	Total DP	Prevalence	Total N	Total with 10% LFU
80%	0.05	0.83	0.71	0.68	0.18	98	0.7	140	156

6.8 Recruitment and Retention

6.8.1 Recruitment

Patients will be identified by the local clinical principal investigator, MDT coordinator, GI specialist nurse or other suitably trained delegated individual via:

- Endoscopy lists
  - Patients provisionally diagnosed with Crohn's based on typical endoscopic findings.
- Outpatient Clinics
- Hospital inpatients
  - For example a new diagnosis presenting acutely and requiring hospital admission
- Multidisciplinary team (MDT) meeting
- Requests for small bowel imaging investigations
  - All imaging requests require justification and will be vetted by the radiologist at each site for the few patients not identified as above

Each recruitment site will allocate dedicated MRE and USS slots for trial patients.

Screening log and subsequent participant withdrawal

An anonymised screening log will be kept of all eligible patients who are approached; reasons for non-recruitment (for example contraindication to MRE or patient refusal) will be provided. This will enable comparisons with the recruited study cohort to ensure the latter is representative of the target patient population, and also provide data on the percentage of patients in whom MRE cannot be performed.

6.8.2 Retention

In order to avoid non-compliance with the study schedule of assessments, patients will be contacted by the Research Fellows and Research Nurse in order to remind them of their MRE/USS appointment date and time and to remind patients to return questionnaires to site

6.9 Data Collection, Management and Analysis

6.9.1 Data Collection Methods

Data will be collected on CRFs by the research nurse staff and collaborators with appropriate training in CRF completion. CRFs will be provided to recruitment sites by the CCTU and stored locally.

As far as lab tests are concerned, the CRP and calprotectin will be measured by local laboratories with their own internal QA process, which will be applied for the purposes of this trial

6.9.2 Non-Adherence and Non-Retention

Outcome data will be collected from all recruited patients undergoing both trial imaging tests according to the protocol.

CRFs will capture information regarding non adherence to protocol stipulations (eg questionnaire completion, provision of stool sample and blood tests) and a list of Protocol Deviations maintained.

Patients will be replaced if they withdraw consent for collection and collation of follow up clinical data to inform the 6 month reference standard.

6.9.3 Data Management

Any completed questionnaires (which will be anonymised) will also be retained for no more than 5 years in a locked room and will be shredded at the end of this time period. Pseudo-anonymised Images, from patient's MRI and USS will be stored on a private company's computer (Biotronics).

A member of the local research team will collate 6 month follow up data on recruited patients to inform the 6 month reference standard panel review and for later effectiveness calculations. In particular, data will be collated on trial CRFs pertaining to imaging scans performed (and their major findings), outpatient visits, inpatient stays, day case attendances for medications, surgical procedures and post mortem findings (if applicable). Hospital clinical data repositories and radiology information systems will be used to collate this data. Imaging scan data, histopathogical data and clinical outcome data will be collated for the at or after 6 months consensus panel review held at each recruitment site for locally recruited patients using secure data transfer systems used in routine NHS clinical practice (including secure NHS email, encrypted CD, encrypted NHS ePACS eg http://www.imageexchange.co.uk 3D). The information stored will be held securely and will be handled according to data protection guidelines.

Biotronics: scan images will be sent in a pseudoanonymised fashion with trial number by CD to UCLH where they will be uploaded by a member of the research team to the Biotronics 3DNet Medical system.

Biotronics has the following systems in place to ensure confidentiality.

- Access is granted only to authenticated named users with a username and password.
- Authentication uses the highest industry standards – VeriSign 256bit SSL extended validation.
- While images and associated reports are viewed, no data is downloaded locally / to the client.
- All users and events are fully audited while using the system.
- 3Dnet Gateway's transmission protocol, between the cloud and institution, uses 2048bit encryption. 3Dnet Gateway manages an intelligent connection that detects and recovers from faults in the line ensuring data in transit is moved without loss and data quality remains fully diagnostic. The 3Dnet Gateway only moves a copy of data; with the original data still remaining onsite.

Patient medical information will be stored in their notes and on NHS computers as with standard care practise. Patients will be provided a study specific identification number, which will render all data pseudonymous. Electronic data will be stored on password-secured UCL and UCLH computers and paper documents in locked cabinets, the key held securely at site.

The people involved in the consensus meetings will review patient data, some of which will contain personal data. These meetings will take place at each of the recruitment sites and only patients who were recruited and/or scanned at the imaging hub/ recruitment site where the meeting is taking place will be reviewed.

The panel will consist of members of the trial research team, including (but not exclusively) those from the recruitment site, the CI and staff from UCL CCTU. All of the members will either have access to the patients' personal data as part of their care team, or as members of the trial research team.

6.9.4 Statistical Methods

6.9.4.1 Statistical Analysis Plan

A separate Statistical Analysis Plan will be produced and finalised prior to data lock and transfer to trial statistician.

Analysis will be based on all patients in the study. The primary and secondary outcomes will be based on available case analysis with a sensitivity analysis using multiple imputation, best case and worst case analysis.

Analysis for the primary outcome will use logistic regression of paired binary outcomes for comparison of diagnostic accuracy measures of MRE and USS within patients, allowing adjustment for clustering by centre. 95% confidence intervals will be calculated and p-values of <0.05 will be 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. STATA statistical software will be used.

Summary of outcomes addressing three diagnostic endpoints by disease groups

1ry outcome= primary outcome

2ry = secondary outcome, with # referring to secondary outcome number

sens = difference in sensitivity

spec = difference in specificity

Diagnostic endpoints	Small bowel Crohn's disease only	Small bowel and colonic Crohn's disease	Colonic Crohn's disease only
Identification and localisation of disease (both active or inactive)	1ry outcome (sens only, per patient) • subgroup new and relapse patients 2ry #1 spec per patient. • subgroup new and relapse patients	2ry #1 additional analyses • subgroup new and relapse patients	

Identification of active disease	2ry #2 (i) per patient (ii)TI segment • subgroup new and relapse patients		2ry #2 additional (iii) (a) per patient (b) per colonic segment • subgroup new and relapse patients
Identification of disease (active or inactive)	2ry #3 subgroup (i) per patient and (ii) per TI segment • subgroup new and relapse patients	2ry #3 (i) per patient (ii) per TI segment • subgroup new and relapse patients	2ry #3 (iii) per seg in colonoscopic reference only group • subgroup new and relapse patients

6.9.4.2 Statistical Methods – Outcomes

6.9.4.2.1 Primary Outcome

Difference in sensitivity per patient of MRE and USS as diagnostic tests for the correct identification and localisation of small bowel Crohn's disease.

- Ability to detect presence of disease (both active and inactive disease)
- Small bowel is defined in this study as proximal small bowel (duodenum, jejunum) and distal small bowel (ileum, terminal ileum)
- Both USS and MRE will be compared with regard to sensitivity based on a reference standard defining disease status for each patient by consensus at or after 6 months committee reviewing all information available for each patient.
- Sensitivity is defined as the proportion of patients with disease by the index test (MRE or USS) compared to those identified with the reference standard.
- Values of sensitivity for both tests will be reported alongside each analysis
- Subgroup analysis will be conducted for separate populations of new versus relapse patients

Definition of disease localisation by USS and MRE

- MRE and USS imaging CRF report from radiologist will report presence or absence of disease regardless of current disease activity status. Disease present but currently inactive will be at deemed present in a particular bowel segment
- WB-MRE imaging CRF report from the WB-MRE radiologist will express presence of small bowel Crohn's disease for each segment and patient categorised as yes, equivocal and no.
- Equivocal results will be grouped with positive test results as these results require additional follow-up investigations compared to negative results.
- Radiologist evaluations for the purpose of the study will be blinded to results of other imaging and non imaging tests, but unblinded to patient status as a newly diagnosed or relapse patient.

- Definitions of disease location are described in the protocol in Section 6.4.1.3 on Blinding of trial Imaging, subsection C Reporting of trial imaging.
- For the purposes of data recording, the bowel will be divided into duodenum, jejunum, ileum, terminal ileum and colon (rectum, sigmoid, descending colon, transverse, ascending and caecum). The jejunum will be defined as the proximal bowel lying largely to the left of a diagonal drawn from the right upper quadrant to the left lower quadrant demonstrating a typically feathery fold pattern. The terminal ileum or neo terminal ileum in the case of past resections will be defined as the last 10cm of small bowel upstream of the ileo-colonic junction. Contiguous disease involving the terminal ileum but extending beyond 10cm will still be classified as terminal ileal disease (as opposed to both terminal ileal and ileal). Distinct sections of disease within a particular bowel segment will be defined as non-contiguous ie discrete locations) if 3cm or more of normal appearing small bowel is present between disease sites. Disease sections separated by less than 3cm of normal bowel will be considered a single disease location

Definition of positive test result from reference test

The reference standard will be established by consensus panel review at or after 6 months

- All test results at 6 months will be considered as part of the reference standard
- This will include third test results, where an additional test is ordered because results from USS and MRE are discrepant in the identification of disease to establish disease status for all small bowel segments (duodenum, jejunum and ileum, terminal ileum)

- Test results will include from the following tests according to their availability: MRE, USS ileo-colonoscopy, capsule endoscopy, imaging, histopathology, HBI, CRP, calprotectin, surgery if available. Blood test results will be considered both at baseline and post therapy follow up at 3 months.

Example reference tests: by type of participant

	Newly diagnosed patients	Relapse patients
Colonoscopy	all	approx 30%
Conventional imaging (may include BaF, CT enterography, capsule endoscopy)	some	some
Third test ordered if USS and MRE give discrepant results	some	some
HBI	all	all
Blood tests (CRP & calprotectin)	all	all

Example reference tests: by disease location

	Whole patient only	Duodenum	Jejunum	Ileum	Terminal Ileum
Colonoscopy					Y
BaF		Y	Y	Y	Y
CT enterography		Y	Y	Y	Y
Capsule endoscopy		Y	Y	Y	Y
HBI	Y activity				
CRP	Y activity				
Calprotectin	Y activity				

Definition of agreement with the reference standard

- Patients will have results recorded for USS, MRE and reference standard according to each segment of small bowel where disease is identified regardless of the disease status as active or inactive.

- An example is shown below for results for a hypothetical patient
- The agreement to reference standard needs to be for the correct locations for all the disease found in the reference standard. A disagreement in either the site of location or the number of sites involved would result in a FN or FP result. For example A, agreement to reference standard is shown by disease presence and disease extent.
- If the index test detected only one area of disease correctly this would be classified as disagreement to reference test. This is because different clinical management could result (e.g. balance of surgery vs medication) if one of two areas of disease were identified.
- If MRE and USS are concordant for the presence of isolated proximal small bowel disease but differ in segmental location (e.g. ileum versus jejunum), the recruitment site clinical and radiological teams will review the imaging and opine if the tests are in fact likely concordant (i.e. the same abnormality has been detected) or likely discordant i.e. true disagreement about the presence of absence of disease in a segment in which case a third arbiter small bowel imaging test would be indicated.
- A table summarising the definition of agreement with reference standard is shown.

Example A table of results from one patient

Small bowel segment	USS	MRE	Reference Standard
Duodenum	N	N	N
Jejunum	Y	Y	Y
Ileum	Y	Y	Y
TI (terminal ileum)	N	Y	Y
Agreement to reference			
Disease presence	Y	Y	.
Disease extent	N	Y	.

Definition of agreement with reference standard

Primary outcome: Test accurate for disease extent	Correct identification of disease presence	Test accurate for disease extent?
Y	Yes –disease identified	Yes-all segments identified
N	Yes –disease identified	No- one or more segments missed
N	Yes –disease identified	No- incorrect segment(s) identified
N	N- no disease identified	No disease identified

Reduction of selection bias

- Recruitment sites would be selected via BSGAR to provide a range of diagnostic pathways representing current NHS practice (eg notably with emphasis on BaF, CT etc as first line tests).
- This has 2 main advantages (i) patients can be recruited with their "confirmed" diagnosis prior to undergoing MRE and USS, making data collection "cleaner" (ii) these conventional tests can be used as part of the later standard of reference to reduce incorporation bias.

- A small number of sites who use MRE or USS as their main first line would also be included.

Handling missing data

Multiple imputations will be used for sensitivity analysis on the impact of missing data using chained equations in STATA (Ian R. White 2011). Best case and worst case analyses will be reported.

Sensitivity analysis

Sensitivity analyses will be carried out

- Classification of equivocal imaging results from USS and MRE as negative test results

Subgroup analyses

Subgroup analysis will be conducted for separate populations of new versus relapse patients

Patient subgroups are defined as follows:

- Newly diagnosed Crohn's disease patients: diagnosis within 3 months of baseline
- Relapse patients: Those with previously confirmed Crohn's disease who are highly suspected of luminal relapse, requiring radiological investigation.

6.9.4.2.2 Secondary Outcomes

SECONDARY OUTCOME #1

Difference in specificity of MRE and USS for correct identification and localisation of small bowel Crohn's disease per patient.

- Ability to detect presence of disease (both active and inactive disease)
- Both USS and MRE will be compared with regard to specificity based on a reference standard defining disease status for each patient by consensus at or after 6 months committee reviewing all information available for each patient.

- Specificity is defined as the proportion of patients with no disease by the index test (MRE or USS) compared to those identified with no disease by the reference standard.
- Values of specificity for both tests will be reported alongside each analysis

- Additional analyses will be included to extend patient population to include both small bowel and colonic Crohn's disease for per patient analysis of (i) the difference in sensitivity and (ii) difference in specificity. For these analyses the same definitions are used as in the primary outcome and secondary outcome #1.
- Values of sensitivity and specificity for both tests will be reported alongside each analysis

Subgroup analysis

For all analyses subgroup analysis for separate populations of new versus relapse patients will be reported.

SECONDARY OUTCOME # 2

Comparison of USS and MRE to detect patients with active small bowel Crohn's disease

(i) Difference in sensitivity and specificity per patient

(ii)Difference in sensitivity and specificity of terminal ileum segment in subgroup of patients undergoing colonoscopy

(iii) Additional analysis in colonic Crohn's for patients with colonoscopic reference for

(a) Difference in sensitivity and specificity per patient

(b) Difference in sensitivity and specificity of colonic segments

- Values of sensitivity and specificity for both tests will be reported alongside each analysis
- Subgroup analysis for separate populations of new versus relapse patients

Reference standard

Per patient: Reference standard

- Full reference standard by consensus panel review at or after 6 months of ileo-colonoscopy, capsule endoscopy, imaging, histopathology, surgery if available, HBI, CRP, calprotectin including post therapy followup.
- HBI, CRP, calprotectin at baseline and 3 months post therapy follow up

Thresholds for per patient presence of active disease

Disease activity will be classified as active or inactive using a combination of Harvey Bradshaw index, CRP, calprotectin and endoscopy (if available).

- Active disease will be deemed to be present if HBI ≥5 (includes 5), and/or raised CRP >8 mg/L , and or raised calprotectin > 100 mg/kg and/or the presence of mucosal ulceration at endoscopy, and/or histopathological evidence of acute inflammation based on biopsy or surgery within 2 months of trial imaging

Terminal ileal: Reference standard

- Patients undergoing colonoscopy as part of usual clinical practice will often have a photograph of the terminal ileum taken by the endoscopist, as well as biopsies of the colonic and small bowel mucosa. Recruited patients will give consent for the photograph and biopsies (if taken) to be used by the trial team to assign their disease status and activity
- The presence of active disease in the terminal ileum will be assigned by the consensus panel review based on the presence of ulceration on the endoscopic photograph (if available) and histological analysis of biopsies by the site histopathologist using a simplified activity score
- Further information if available will be included from additional colonoscopy or surgery

Definition of active disease by USS and MRE

MRI

At least one of wall thickening/ increased mural signal/increased mesenteric signal / increased enhancement (mucosal or layered) OR ulceration OR abscess

USS

At least one of wall thickening/ focal hyperechoic mesentery (With or without fat wrap)/ / isolated thickened (increased thickness compared to mucosa of normal bowel in the same patient /ill-defined submucosal layer/ ill-defined anti-mesenteric border/ Increased Doppler vascular pattern OR ulceration OR abscess

- Reporting radiologists will state if, in their opinion and based on these criteria, any disease present is active or non-active on a segmental and per patient basis.

Disease active (A) vs inactive (I): Example A table of results from one patient

Outcome	USS	MRE	Reference per patient activity (HBI, CRP, calprotectin, conventional tests)	Reference per segment (conventional tests)
Any active disease present	A	A	A	A
Active disease in TI (terminal ileum)	I	A	.	A
Agreement to reference				
Presence active disease	Y	Y	.	.
Presence active disease in TI	N	Y	.	.

Additional analysis

Additional analyses in colonic Crohn's disease for patients with colonoscopic reference for presence of active disease

(a) Difference in sensitivity and specificity per patient

(b) Difference in sensitivity and specificity of colonic segments

As the six colonic segments can be harder to distinguish, agreement to colonic reference standard will allow for this. Rules to judge segment agreement will be defined in the full Statistical Analysis Plan.

Subgroup analysis

A subgroup analysis will be conducted for separate populations of new versus relapse patients

SECONDARY OUTCOME #3

Comparison of USS and MRE diagnostic accuracy to detect presence of disease (either active or inactive

(i) Difference in sensitivity and specificity per patient in small bowel and colonic Crohn's disease

(ii) Difference in sensitivity and specificity of terminal ileum segment in subgroup of patients undergoing colonoscopy in small bowel and colonic Crohn's disease

(iii) Difference in sensitivity and specificity per segment in subgroup of patients undergoing colonoscopy in colonic Crohn's disease

- Values of sensitivity and specificity for both tests will be reported alongside each analysis
- Subgroup analysis for separate populations of new versus relapse patients
- Subgroup analysis for small bowel Crohn's only for (i) and (ii)

Example A table of results from one hypothetical patient

Outcome	USS	MRE	Reference Standard: per patient	Reference Standard: per terminal ileum	Reference Standard: colonoscopy
Presence of disease (active or inactive) in any small bowel or colon segment	N	Y	Y		
TI (terminal ileum): Presence of disease (active or inactive)	N	Y	Y	Y	Y
Per segment analysis(iii): Colonoscopic reference only Total number of diseased regions (active or inactive)	0	2			2
Agreement to reference					
Disease presence	N	Y	.		
TI disease present	N	Y	.		
Per segment analysis(iii): Colonoscopic reference only Number of diseased colonic segments	N	Y	.	.	

Subgroup analysis

Subgroup analysis for

(i) Separate populations of new versus relapse patients

(ii) Small bowel Crohn's only for difference in sensitivity and specificity per patient and difference in sensitivity and specificity of terminal ileum segment.

SECONDARY OUTCOME #4 Patient management

Patient management will be reported at clinical site meetings.

- At each site visit a single set of test results for an individual patient will be revealed and diagnoses and patient management recorded.
- For each patient the order of revealed test results (USS, MRE, conventional tests, all tests) will be randomised with meetings for each test being at least 4 weeks apart to reduce recall bias.
- The patient management plan based on all tests will be used as a reference test for patient management decisions.

Patient management will be recorded using pre-defined categories detailed in the CRF proforma Options will be based on the following but will be finalised for CRFs prior to trial recruitment

- Patient is on no small bowel medication and none will be added
- Patient is on no small bowel medication but will be started on some
- Maintain current small bowel medication
- Reduce dose of current small bowel medication
- Increase dose of current small bowel medication
- Stop current small bowel medication
- Change current small bowel medication to similar drug class (eg conventional or biological)
- Change current small bowel medication to different drug class (eg from conventional to biological)
- Refer for surgical therapy
- Other (please state)

Patient management decisions will be grouped following clinical input into a small number of categories as detailed in the Statistical Analysis Plan. The groupings will be finalised before data lock and transfer to trial statistician.

A subgroup analysis will be completed for separate populations of new versus relapse patients.

SECONDARY OUTCOME #5

- The lifetime incremental cost and cost-effectiveness of assessment using MRE and USS compared to each other, and to conventional imaging.

SECONDARY OUTCOME #6

- Diagnostic accuracy and radiologist confidence using hydrosonography compared to conventional USS
- A substudy will be conducted to evaluate the incremental benefit in diagnostic performance of hydrosonopgraphy compared to conventional USS.

Comparison of diagnostic accuracy of WB-MRE alone using (i) conventional USS (ii) hydrosonopgraphy.

- Difference in sensitivity and specificity
    - Per patient
    - Per segment (TI only)
    - Subgroup analysis for separate populations of new versus relapse patients
- Difference in diagnostic confidence

Reference standard: Full reference standard by consensus panel review at or after 6 months of ileo-colonoscopy, capsule endoscopy, imaging, histopathology, HBI, CRP, calprotectin including post therapy followup.

SECONDARY OUTCOME #7

- Comparative patient experience of MR and USS

SECONDARY OUTCOME #8

- Diagnostic impact of novel MRE sequences, notably diffusion weight imaging on disease detection, diagnostic confidence and disease activity assessment.

The objective is to evaluate the incremental benefit in diagnosis of novel MRE protocols notably diffusion weighting and contrast enhanced imaging compared to more standard MRE protocols.
Comparison of diagnostic accuracy of WB-MRE alone using (i) conventional True FISP (ii) diffusion weighted (iii) contrast enhanced imaging.

Percentage of patients in which alternative imaging sequences were

- Classified as helpful
- Increased diagnostic confidence but diagnosis unchanged
- Changed diagnosis for presence of disease (i) additional disease site detected (ii) disease site discounted
- Changed diagnosis for diagnosis of active disease (i) additional active disease site detected (ii) active disease site discounted
- Descriptive analysis of additional comments on comparison of MRE sequences.

- For difference between imaging methods: Confidence intervals will be calculated for paired proportions using Newcome method (Newcome 1998).

SECONDARY OUTCOME #9

Inter-observer variation in the evaluation of MRE and USS datasets by radiologists, and to assess the impact of diagnostic confidence on accuracy

A substudy will be conducted to look at inter-observer variability between radiologists in the evaluation of MRE and USS datasets and the effect of diagnostic confidence on diagnosis.

Hub radiologists will interpret a sample of approximately 20 MRE datasets selected at random from the other imaging hubs to define inter-observer variation in the reported presence of disease and disease activity.

These images will be read after patient management decisions are taken and so will not affect patient diagnosis or treatment.

For USS inter-observer variation, approximately 5 patients per site will need to be scanned twice by two radiologists.

6.10 Economic evaluations

Cost effectiveness

We will undertake a detailed analysis of the cost and the cost-effectiveness of the use of MRE and USS compared to each other, and to conventional investigations, in the management of Crohn's disease patients. A separate cost-effectiveness analysis for those newly diagnosed with Crohn's disease and those with suspected relapse will be performed. The analyses will conform to accepted economic evaluation methods (NICE 2008). All costs will be assessed from the perspective of the NHS and personal social services (PSS).

The care pathways for Crohn's disease patients can be divided into two stages, the ***treatment decision pathway*** and the subsequent ***disease pathway***. The former includes the time from (suspected) diagnosis to treatment decision; the latter includes the time period following the treatment decision. The treatment decision pathway will be different between MRE, USS and standard investigations, yielding different costs and potentially different treatment decisions. In patients for whom the treatment decision with MRE, USS and conventional investigations is the same, the subsequent disease pathways will be the same. Where the treatment decision with MRE, USS and conventional tests are different, the treatment disease pathway will be different, yielding potentially different costs and health outcomes. Hence, if in the patients studied the concordance between the treatment decisions associated with MRE, USS and conventional investigations is high, then the economic analysis can focus on the cost of the treatment decision pathways only because the disease pathways will be no different. In this case the cost-effectiveness of MRE and USS compared to each other, and to conventional tests, depends on the incremental cost (positive or negative) of each diagnostic procedure in the treatment decision pathway.

Conversely, if the concordance between the treatment decisions is low, then the economic analysis ought to focus on both the treatment decision pathways ***and*** the subsequent disease pathways. In this case the cost-effectiveness of each diagnosis strategy depends on its incremental cost compared to the other alternatives in the treatment decision pathway plus its incremental costs and health benefits compared to the other alternatives in the disease pathway. The nature of the economic analysis will therefore depend on the degree of concordance between treatment decisions provoked by MRE, USS and conventional investigations.

Discordance will be defined if the first major treatment decision differs between MRE, USS and standard investigations in greater than 5% of patients. We define a major difference in treatment

decision as occurring when only one pathway suggests referral for surgical management or a significant change in medical therapy (introduction of a new agent, reduction in current therapy, or change in medication class such as from non-biological to biological therapy).

Scenario 1. Concordance between the treatment decisions associated with MRE and USS and standard investigations:

In this case, the cost components included in the analysis will be the costs of:

- Conventional investigations (ileo-colonoscopic, histological, clinical and radiological investigations plus additional conventional imaging such as CT and BaF)
- Treating adverse events associated with conventional tests
- MRE, plus additional tests generated by MRE
- Treating adverse events associated with MRE
- USS, plus additional tests generated by USS
- Treating adverse events associated with USS
- MDT meetings/ outpatient visits.

The volume of resource use for each cost component will be measured directly in the study from treatment decisions recorded on the treatment decision CRFs, based on conventional investigations alone, on MRE alone, and on USS alone, and on patient records. Unit costs will be taken from standard published sources. Since the three diagnostic strategies yield the same treatment decisions cost-effectiveness depends on the incremental cost of MRE versus USS, and the incremental cost of both of them versus conventional investigations, in the treatment decision pathway.

Scenario 2. Discordance between the treatment decisions associated with MRE and USS and standard investigations:

In this case, cost-effectiveness depends on the incremental cost (positive or negative) of the treatment decision pathway and disease pathway associated with MRE, USS and conventional investigations and the incremental health benefits (positive or negative). We will calculate cost-effectiveness in terms of the incremental cost per quality-adjusted life year (QALY) gained using 6 months and lifetime horizons.

For the analysis based on the 6-month time horizon the study will provide information on the treatment decisions arising from MRE, USS and conventional investigations and follow-up data for the first 6 months. We will collect these data from two sources. First, we will collect the resource use

data for the main drivers of hospital costs using a study specific CRF. This will collect resource use data on the following cost components for each patient:

- Imaging investigations
- Endoscopy
- Surgery
- Outpatient visits
- Inpatient stays
- Day cases
- Major medication changes

These data will be recorded centrally via the hospital records. Unit costs will be taken from standard published sources and applied to the resource use data, allowing us to cost the care received by each patient.

Second, we will prospectively collect resource use data using patient diaries. This will allow us to collect data on primary and community care contacts. These will record resource use data on the following cost components:

- GP contacts
- Practice and community nurse contacts
- Any other primary care or community care contacts related to Crohn's disease.

The diaries will be given out at baseline and at 3 months and patients will be asked to complete them for the following three month period.

In addition we will also collect data on health-related quality of life score, measured according to the EQ-5D (www.euroqol.org), which will be measured at baseline, 3 months and at 6 months. Patient-specific utility profiles will then be constructed assuming a straight line relationship between each of the patients EQ-5D scores at each follow-up point. The quality-adjusted life-years (QALYs) experienced by each patient up to 6 months will be calculated as the area underneath this profile.

Individual patients will then be grouped according to the specific disease path depending on the treatment decision and the diagnostic accuracy. We will calculate the mean costs and QALYs for

each group. Mean costs and QALYs for MRE versus US and compared to conventional investigations will then be calculated based on the proportion in each group using each algorithm, which will be different since in this scenario there is discordance in treatment decision.

Cost-effectiveness will be calculated as the mean cost difference between MRE versus USS and compared to conventional investigations divided by the mean difference in outcomes (QALYs) to give the incremental cost-effectiveness ratio (ICER). Non-parametric methods for calculating confidence intervals around the ICER based on bootstrapped estimates of the mean cost and QALY differences will be used (Briggs AH. 1997). The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will show the probability that each alternative is cost-effective for different values of the NHS' willingness to pay for an additional QALY. We will also subject the results to extensive deterministic (one-, two- and multi-way) sensitivity analysis.

For the analysis based on the lifetime time horizon we will use the 6 month data described above. To extrapolate beyond the end of the follow-up period we will develop two de novo cost-effectiveness models for the disease pathway, one in patients with newly diagnosed Crohn's disease, the other in patients with suspected relapsed Crohn's disease, which will be populated via available evidence. The models are likely to be similar in design to a recent HTA-funded study of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease (Dretzke J et al 2011). Following decisions about model structure, a list of parameter estimates required for the model will be developed. The specific details of the data to be used to populate the model will be determined following the development of the structure and the systematic searches of the literature to identify existing models.

Input parameters will be assigned probability distributions to reflect their imprecision and Monte Carlo techniques will be used to reflect this uncertainty in the results. In this case, cost-effectiveness depends on the incremental costs and benefits of MRE versus USS versus conventional investigations, and results will be presented in terms of the incremental cost per incremental QALY gained, with appropriate treatment of parameter uncertainty. We will construct cost-effectiveness acceptability curves and cost-effectiveness confidence ellipses and subject the results to extensive deterministic sensitivity analysis. This will identify which parameters in the model are most uncertain and are important drivers of cost-effectiveness.

7 Oversight and Trial Committees

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 UCL 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 Quality Management and Monitoring Plan.

7.1 Trial Committees

7.1.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the UCL CCTU. The TMG will be responsible for the day-to-day running and management of the trial. It will meet at least three times a year at least one of which will be in-person. The full details can be found in the TMG Terms of Reference (ToR).

7.1.2 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) has independent membership, including the Chair plus members from the TMG. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC ToR.

7.1.3 Independent Data Monitoring Committee [IDMC]

An Independent Data Monitoring Committee (IDMC) is the only group who will see the confidential, accumulating data for the trial split by trial arm. Reports to the IDMC will be produced by the trial statistician (Dr Susan Mallett). The IDMC will meet within six months of the trial opening. The timing and frequency of subsequent meetings and any interim analyses and will be stated in the IDMC ToR. The IDMC can recommend premature closure or reporting of the trial to the TSC. Further details of IDMC processes are provided in the IDMC ToR.

7.1.4 Study Sponsor

The sponsor is responsible for securing the arrangements to initiate, manage and finance a study. UCL is the trial sponsor and has delegated the duties as sponsor to UCL CCTU with a memorandum of understanding (MoU).

7.2 Safety reporting

Adverse reactions are not expected within this trial as the intervention is minimal, as per standard of care and well established with a highly developed safety profile. 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 trial. There may be reactions to the contrast agent, gadolinium. As such reactions are well established within the profile there is no added value in reporting them to the REC. If any suspected unexpected serious adverse reactions (SUSARs) occur, these will be reported to the REC within the relevant timeframes. Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

7.2.1 Guidance for Adverse Event Inclusions and Exclusions specific to this trial:

Adverse events/reactions to be reported:

- those which fulfil the definitions of a SUSAR and
- which are related directly to the trial intervention (MRE, USS and arbiter imaging tests performed according to the trial protocol)

Adverse events/reactions NOT to be reported:

- any changes in or complications related to, the patients underlying Crohn's disease or other diagnosis not related to the trial imaging intervention

7.2.3 Other notifiable events

There are no other notifiable adverse events in this trial.

7.2.4 Procedures to follow in the event of participants becoming pregnant

All tests that may be used during the duration of this study (e.g. colonoscopy, barium, MRI, etc) are relatively contraindicated in pregnancy. Pregnancy tests will only be done if they would have been as part of standard of care.

Pregnancy is an exclusion criterion; eligible patients who are recruited will be pregnancy tested, if necessary and as per normal clinical practice, before their MRI scan. Participants who become pregnant during the course of the trial will be treated as per usual standard of care, with the care guided by the pregnancy.

7.2.5 Investigator responsibilities relating to safety reporting to UCL CCTU

All serious adverse events and serious adverse reactions should be recorded in the patient's medical notes. All SUSARs should be documented in the patient notes and notified to the UCL CCTU within 24 hours of the investigator becoming aware of the event.

7.2.6 Notifications

7.2.6.1 Notifications by the Investigator to UCL CCTU

UCL CCTU must be notified of all SUSARs within 24 hours of the investigator becoming aware of the event and must be notified to UCL CCTU until trial closure.

7.2.6.2 UCL CCTU responsibilities

UCL CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs to the REC as appropriate. Fatal and life threatening SUSARs must be reported to the REC within seven days of UCL CCTU becoming aware of the event; other SUSARs must be reported within 15 days. UCL CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

7.3 Quality Assurance and Control

7.3.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the METRIC trial are based on the standard UCL 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.

7.3.2 Central Monitoring at UCL CCTU

UCL 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 trial 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 METRIC 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 trial related monitoring, including audits and REC review, 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.

7.4 Ethics and Dissemination

7.4.1 Research Ethics 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 REC 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 Research and Development (R&D) NHS Permissions.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative investigation 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 trial for the purpose of follow up and data analysis.. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.4.2 Competent Authority Approvals

This is not a clinical trial of an investigational medicinal product, therefore competent authority approvals do not need to be sought.

7.4.3 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 R&D permissions (or other relevant permissions 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 approval and methodological, statistical, clinical and operational input from the UCL CCTU Protocol Review Committee.

7.4.4 Protocol Amendments

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

7.4.5 Consent

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 trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

As this trial 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 patient 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 UCL CCTU Trial Team.

Patients will also be asked to consent to use of their anonymised data and for their anonymised data to be stored and used for future related research.

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

7.4.5.1 Consent in Ancillary Studies

Patients will consent to take part in the following sub-studies, independent from consent to the main trial:

i) Hydrosonography

ii) Interobserver agreement for USS

iii) Heath psychology questionnaires

7.4.6 Confidentiality

The UK Data Protection Act will be followed in this trial.

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 (eg patient details for questionnaire distribution and reminders) will use secure communication approved for such purposes by NHS data protection emails (eg secure NSH email). 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 trial will be registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

7.4.7 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 trial.

7.4.8 Archiving

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

7.4.9 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.

7.4.10 Indemnity and compensation

The analysis of CRP and calprotectin will be met by the research grant and local support costs. Trial imaging costs will be met by local support cost and agreed allocated treatment costs as per local recruitment site agreements. There will be no specific benefit provided to patients after trial completion.

UCL holds insurance against claims from 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 participants. 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 a NHS Trust or otherwise.

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 the Sponsor'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.

7.5 Publication Policy

7.5.1 Trial Results

Data will be presented at national and international conferences and published in peer reviewed journals. Our patient representative with 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. Patients will be informed of the study results during outpatient follow-up appointments.

7.5.2 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 Professor Stuart Taylor and include all TMG members. All TMG members, Trial Manager and Trial Statistician will be authors on the publications and named individually. The TMG will approve addition of other trial investigators on trial related publications as appropriate.

7.5.3 Reproducible Research

Whilst datasets will not be made available without prior consent of the TMG, the protocol will be published, and so made publically available, early in the trial.

8 Sub Studies

A. Diagnostic benefit of oral contrast administration prior to USS ("hydrosonography")

Recruitment sites will be invited to opt into a substudy of hydrosonography. A sample of 75 recruited patients will undergo unprepared USS as per study protocol but in addition undergo hydrosonography following an oral contrast load. The same radiologist will perform both examinations to limit the potential for inter-observer variation. The standard USS CRFs will be completed pertaining to disease presence, location, extent and activity, with diagnostic confidence after each individual examination i.e. without and with oral contrast. The results of both examinations will be compared against the final consensus reference standard, and the additional diagnostic benefit (if any) of an oral contrast load assessed.

Additional consent for participation in the hydrosonography substudy will be obtained from recruited patients. Because of the potential side effects of an oral contrast agent (such as diarrhoea), it is permissible for patients to undergo hydrosonography immediately after their MRI, making use of the oral contrast given for the MRI.
Wherever possible however, preference will be given to performing USS before and after an oral contrast load additional to that used for MRI. In this scenario, patients will ingest the oral contrast over 50-60 minutes prior to the USS. The findings on the standard USS will be used for the purpose of the main trial and primary endpoints. The two USS examinations should ideally be performed on the same day, although a period of 2 weeks between the examinations will be permissible.

B. Inter-observer variation in USS interpretation

If possible, a sample of at least 5 patients at each recruitment site will undergo two USS examinations by two independent radiologists (adhering to the blinding protocols required by the main trial) to define rates of interobserver variation. The report produced by the first reader will be used for the purposes of the main trial; the second review will provide data only for this sub study. The USS CRF pertaining to disease extent, location and activity will be completed by both radiologists independently. The two USS examinations should ideally be performed on the same day, although a period of 2 weeks between the examinations will be permissible. Additional consent for participation in the substudy will be obtained from recruited patients.

C. **Influence of oral contrast agent and ingested volume on small bowel distension during MRI**

Recruitment sites use different oral contrast agents and this will be permitted in the trial. As noted above the nature of the oral contrast will be recorded for all recruited patients and wherever possible the volume ingested prior to the MRI will also be recorded. MRI datasets will be collected centrally allowing retrospective study. A research fellow will grade the quality of small bowel and colonic distension for all datasets devising a grading system after review of the available literature. The quality of distension will them be compared across different oral contrast agents and ingested volume. The patient reported symptoms in the administered questionnaires will also be correlated with distension quality and type of oral contrast agent

D. **Contribution of contrast enhanced and diffusion weighted imaging to MRI evaluation**

As noted in section 6.4.1, reporting radiologists will prospectively note on the MRI CRF the benefit, if any, of contrast enhanced and diffusion weighted images over conventional T2 weighted images.
A retrospective reader study using the centrally collected anonymised MRI datasets will be performed. Participating radiologists (up to 15) will review the MRI datasets using a locked sequential viewing paradigm. Using the MRI CRF, radiologists will analyse the MRI datasets using just T2 weighed and TruFISP sequences. They will then review the diffusion weighted images, re-completing the CRF before finally reviewing the contrast enhanced sequences and completing the final 3rd CRF. Reporting times for each sequence block will also be recorded. The influence of diffusion weighted and contrast enhanced images on radiologist diagnostic accuracy (compared to the consensus reference and diagnostic confidence) will be assessed.

E. Inter-observer variation in MRI interpretation

Each radiologist (n=12) will read a sample of 20 studies acquired and interpreted at a different site in order to define rates of inter-observer variation. MR examinations will be uploaded to the central image server used for image storage during the trial (3D net), which will facilitate these interpretations, which take part over the course of the study. Radiologists will read scans acquired at other recruitment sites to reduce recall bias for their own patients. Proformas detailing disease extent, location and activity will be completed.

F. **Influence of radiologist diagnostic confidence on MRI and USS accuracy**

Interpretation confidence (scored 1-6 by reporting radiologists) scores will be related to diagnostic accuracy.

9 Protocol Amendments

Update to Version 7.0 of the protocol has been submitted to add the closure of the relapse arm of the study now it has reached its target recruitment, changes to staffing on the IDMC and on to the trial team at the CCTU. There have also been the following changes to the modelling of therapeutic impact sub study: clarification that each site will attempt to complete the process for 20 patients, but are allow to do more cases if resources allow; clarification that Priority will be given to patients for who the findings of MRE, USS and / or clinical testing are discrepant; changes to the time reviews for each imaging modality and will be at least 2 weeks; adaptions to the process of reviews so that they can be done electronically by the gastroenterologist with involvement of the radiologist if required.

Version no.6 of the protocol clarified an existing part of the protocol with regard to the retrospective use of relevant clinical data acquired prior to formal patient written consent to take part in the study. The protocol has always stated that use of prior clinical data is required (with patient consent) for two main reasons (i) to reduce the burden on patients having to undergo repeat testing, for example blood, stool or imaging when such tests have been performed recently as part of usual clinical care and are perfectly acceptable for use in the trial and ii) to help inform the consensus committee after 6 month patient follow up when the reference standard for disease status is defined. For example knowledge of the findings of colonoscopy performed prior to recruitment is useful when reaching a final consensus diagnosis.

Version 5.0 of the Protocol has been provided to mainly inform of a substantial amendment to the review process regarding the data collected for the Diagnostic and Therapeutic Impact sub-study to suggest that sites will be reviewing data collected at other recruitment sites. Another substantial amendment provided with this protocol is related to the expected volume of sites' recruitment into the Inter-observer variation in USS interpretation sub-study, as 'ideally' now been added before expecting sites to recruit a sample of at least 5 patients each for this sub-study.
The non-substantial amendment provided in this version of the protocol includes a change related to the timing of the consensus panel which we now suggest could be conducted at or after 6 months instead of at 6 months. The amended protocol also includes some administrative revisions.

Version 4.0 of the Protocol was provided to remove the requirement for the patients to have at least 24 hours to review the Patient information sheets prior to consent if they feel they been sufficiently informed

Version 2.0 of the Protocol was provided to include Sonographers to carry out scans as part of the research team. The amendment also included some minor administrative changes

Version 1.0 of the protocol was the initial Protocol reviewed and approved by the Research Ethics Committee prior to commencing the study.

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11 Appendices

11.1 Appendix 1: MRI sequence protocol

Minimum *	Optional
Coronal true FISP	Axial True FISP
Buscopan-20mg IV	Axial Fat Sat HASTE
Axial and coronal non Fat Sat HASTE	Axial post gadolinium T1
Coronal Fat Sat HASTE	True FIP dynamic Motility
Axial diffusion b values 50 and 600	
Coronal pre and post gadolinium T1 (60-70 sec)	

* equivalent sequences permissible according to MRI manufacturer

11.2 Appendix 2: Minimum Ultrasound protocol

Nil by mouth- 4 hours

Use of both curve-linear and high resolution probe (min 5Mhz frequency)

Systematic review of colon and small bowel with both probes

Review of enteric tissues

Application of colour Doppler (typical flow 6-9m/s)

11.3 Appendix 3: Imaging definitions of active disease

MRI

At least one of: wall thickening/ increased mural signal/increased mesenteric signal / increased enhancement mucosal or layered) OR ulceration OR abscess

USS

At least one of: wall thickening/ focal hyperechoic mesentery (with or without fat wrap)/ / isolated thickened (increased thickness compared to mucosa of normal bowel in the same patient /poorly defined submucosal layer/poorly defined anti-mesenteric border/ increased Doppler vascular pattern OR ulceration OR abscess

11.4 Appendix 4-Harvey Bradshaw index

Reference: (SANDBORN JS 2002)

STUDY TITLE:

PRINCIPLE INVESTIGATOR:

Thank you for agreeing to participate in this research study. Before you fill in the diary below it is important that you have read the Patient Information Sheet and the Informed Consent Form.

Symptom questionnaire
Instructions

Column A: please fill in the date

Column B: please fill in the number of liquid or very soft stools (motions) you have passed that day. For example if you have gone 5 times and two were 'normal' formed motions you would write down 3

Column C: please circle the number that most closely matches the worst pain you have felt all day (0 = none; 1 = mild; 2 = moderate; 3 = severe)

Column D: please circle the number that most closely matches how well (or unwell) you have felt during the day (0 = generally well; 1 = a bit under par; 2 = poor; 3 = very poor; 4 = terrible)

Column E: please circle 'Yes' if you have taken any medications to try and slow down your bowels (e.g. 'Imodium' (loperamide), Lomotil, codeine phosphate or any pain killers containing codeine such as cocodamol, codydramole, dichydrocodeine, DF118). If you take any pain killers for pain this does not count and you would circle 'No'. If you did not take anything to slow down the bowels then also circle 'No'

Column F: this only needs to be filled in if you have felt you have had a temperature (fever) and used a thermometer to find out

If you have any questions about how to fill in the diary, please contact:

Study number		**Initials**	

	A	B	C	D	E	F
Day	**Date**	**Number of liquid or very soft stools**	**Abdominal pain rating (circle)** **0 = none** **1 = mild** **2 = moderate** **3 = severe**	**General wellbeing (circle)** **0 = generally well** **1 = a bit under par** **2 = poor** **3 = very poor** **4 = terrible**	**Were anti-diarrhoeals taken? (circle)** e.g. loperamide, codeine phosphate or lomotil	**Temperature**
MRI			0 1 2 3	0 1 2 3 4	Yes / No	

TO BE COMPLETED BY DOCTOR or trained nurse

Date of assessment	
Height (cm)	
Weight (kg)	
Arthritis present? *(circle one)*	**No / Yes**
Iritis or uveitis present? *(circle one)*	**No / Yes**
Erythema nodusum, pyoderma gangrenosum or aphthous stomatitis present? *(circle one)*	**No / Yes**
Anal fistula, fissure or abscess present? *(circle one)*	**No / Yes**
Other fistula present? *(circle one)*	**No / Yes**
Abdominal mass present? *(circle one)*	**No / Questionable / Yes / Yes and tender**
HCT	
NAME of assessor capitals)	
SIGNATURE	

11.5 Appendix 5:Histological grading of Terminal ileum Biopsies

Histological Activity Index (HAI)		
Inflammatory activity	***Score***	***Histological findings***
Inactive / Quiescent	0	No intraepithelial neutrophils
Mildly active	1	Neutrophils <50% of crypts, no ulcers or erosions
Moderately active	2	Neutrophils >50% crypts, no ulcers or erosions
Severely active	3	Erosions or ulceration, irrespective of other features

Comprehensive Activity Index

Histology	Score
Architectural changes (villous/crypt architecture)	0 – No abnormality 1 – Mild abnormality 2 – Mild / moderate abnormality or multifocal 3 – Severe diffuse or multifocal abnormalities
Chronic inflammatory infiltrate	0 – No increase 1 – Mild but unequivocal increase 2 – Moderate increase 3 – Severe increase
Acute inflammatory infiltrate	Eosinophils A.0 – No increase A.1 – Mild but unequivocal increase A.2 – Moderate increase A.3 – Severe increase Neutrophils: B.0 – No increase B.1 – Mild but unequivocal increase B.2 – Moderate increase B.3 – Severe increase
Neutrophils in the epithelium	0: None 1: <5% of crypts 2: 5-50% of crypts involved 3: >50% of crypts involved
Crypt destruction	0: None 1: probable (local excess of neutrophils in part of crypts) 2: Probable – marked attenuation Unequivocal crypt destruction
Ulceration:	0: No erosion, ulceration / granulation tissue 1: Regenerative epithelium adjacent to inflammation 2: Early erosion 3: Unequivocal erosion 4: Ulcer or granulation tissue
Granulomas	Yes or No

11.6 Appendix 6: MRI QA score

Technical quality-general
1= More than one sequence with substantial degradation of images severely limiting interpretation of those sequences, and not repeated
2= One sequence with substantial degradation of images severely limiting interpretation of that sequence, and not repeated
3= More than one sequence has minor artefact, but all remain fully diagnostic and repeat although optimal, not necessary OR all sequences initially technically inadequate (score 1 or 2) correctly repeated
4= One sequence a has minor artefact, but remains fully diagnostic and repeat, although optimal, not necessary
5= All sequences technically optimal with no artefact or degradation

Technical quality-anatomical coverage
1= Wrong examination performed
2= More than one sequences does not adequately cover the body (whole small bowel and colon)
3= One sequence does not optimally cover the small bowel and colon but examination remains fully diagnostic
4= All sequences optimally cover the small bowel and colon