Research Study Protocol

Department of Rheumatology, Cambridge University Hospitals NHSFT

Magnetic resonance enterography as a screening tool for axial spondyloarthritis in Crohn's disease: A prospective single-center cross-sectional observational study using MRE screening followed by clinical assessment (ProSpA-CD)

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IRAS Ref: 249724

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Protocol Version 3; 18 Sept 2018

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TABLE OF CONTENTS

1. Protocol summary

1.1 Title of study

Magnetic resonance enterography as a screening tool for axial spondyloarthritis in Crohn's disease: a prospective single-center cross-sectional observational study using MRE screening followed by clinical assessment.

1.2 Aim

The aim of this study is to determine the sensitivity and specificity of magnetic resonance enterography (MRE) as a screening tool for axial spondyloarthritis (axSpA) in a cohort of adult patients with Crohn's disease (CD) in a secondary-care hospital, using dedicated axial magnetic resonance imaging (MRI) with clinical assessment as the gold standard.

1.3 Objectives

We hypothesise that existing cross-sectional imaging (MRE) from the routine NHS care of patients with CD can be used to screen patients for evidence of axSpA, thereby prompting onward referral to the rheumatology department for further management.

The objectives of this study are therefore to determine:

1. the validity, sensitivity, specificity and area under the receiver operating characteristic (ROC) curve (AUC) of MRE as a screening tool for axSpA in CD, using dedicated axial MRI scans with clinical assessment as the gold standard.

2. the proportion of patients with evidence of axSpA on MRE imaging who fulfill the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA, modified New York criteria for ankylosing spondylitis (AS) and the classification criteria for psoriatic arthritis (CASPAR).

3. the proportion of these patients proceeding to non-pharmacological and pharmacological treatment of their axSpA, as a surrogate measure of change in clinical care as a result of MRE screening.

4. the extra-articular features associated with axSpA in CD, in order to better characterise the clinical phenotype of enteropathic spondyloarthritis (eSpA).

5. whether the site of CD (colon, ileum, *etc*.) predicts the occurrence of axSpA.

1.4 Design

Prospective single-center cross-sectional observational study

1.5 Study group

The ProSpA-CD study will be divided into two parts:

ProSpA-CD-Screen Phase: Review of the patients MRE scan for evidence of axSpA
The gastroenterology team (Drs Raine and Parkes) at Cambridge University Hospitals (CUH) will write to approximately 1100 patients with a diagnosis of CD (male and female patients aged 18 years or above) who have had a MRE scan since 2015, asking for their consent to retrospectively review the MRE scans for evidence of axSpA. CD subjects with a known diagnosis of SpA (AS, axSpA, eSpA or

psoriatic arthritis) will be eligible and invited to enter the study. Subjects who consent to this will then have their MRE scans reviewed for this purpose.

ProSpA-CD-Assess Phase: Clinical assessment of case and control subjects for evidence of axSpA in the clinic setting

Patients with lesions on their MRE scan consistent with axSpA (regarded as 'cases'), but who do not have a known diagnosis of SpA, will be referred for further clinical assessment in the NHS rheumatology spondyloarthritis (SpA) clinic for evidence of axSpA (Dr Jadon's NHS SpA clinic, but assessed by Dr Evans in a supernumerary capacity). Patients will also be invited to participate in the ProSpA-CD-Assess phase of the study at this stage.

CD subjects with a known diagnosis of SpA who are already under review by rheumatology and who have lesions on MRE consistent with axSpA will be considered as cases but will instead be invited to attend the rheumatology SpA research clinic to be assessed for axSpA as this will be considered outside of their routine NHS care (Dr Jadon's SpA research clinic, but assessed by Dr Evans in a supernumerary capacity).

CD subjects (including those with a known diagnosis of SpA) who had consented to have their MRE scans reviewed, but do not have evidence of axSpA on MRE will also be invited to participate in this phase of the study as 'control' subjects and consenting subjects will be referred for further clinical assessment in the rheumatology SpA research clinic for evidence of axSpA (Dr Jadon's SpA research clinic, but assessed by Dr Evans in a supernumerary capacity). Cases and controls will be matched for sex and age, with a cases : control ratio of 1:1.

1.6 Study schedule

The MRE scans of consenting patients will be reviewed for evidence of axSpA in the ProSpA-CD-Screen phase of the study. Case and control subjects meeting the inclusion criteria and giving informed consent as per section 5.2.2 will then be recruited in to the ProSpA-CD-Assess phase of the study. Consented subjects will complete the following patient reported outcome measures (PROM); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), a Visual Analogue Score for back pain (VASbp), Ankylosing Spondylitis Disease Activity Score (ASDAS) and Stanford Health Assessment Questionnaire Disability Index (HAQ-DI). Each subject will be examined in the SpA clinic using the Bath Ankylosing Spondylitis Metrology Index (BASMI), 68 tender joint count, 66 swollen joint count, the spondyloarthritis research consortium of Canada (SPARCC) enthesitis index, and for skin or nail psoriasis.

The following investigations will also be performed *as per* standard of care for the patients with axial skeleton abnormalities on their MRE (MRE+) and no known diagnosis of SpA, if clinically indicated and if not been performed in the preceding month; full blood count (FBC), renal function, liver function tests (LFTs), C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR) and faecal calprotectin. *HLA-B27* testing will also be requested if not previously performed. These investigations will also be performed for the control subjects and the group of CD subjects with a known diagnosis of SpA who are MRE+ (if not performed in the preceding month and if *HLA-B27* not previously performed) but will be funded by the research grant, unless clinically indicated.

A dedicated axial MRI scan of the spine and sacroiliac joints will be performed in all case and control subjects if indicated by the clinical assessment as part of their standard NHS care. Subjects in whom a dedicated axial MRI scan is not clinically indicated, or those who have had one performed previously for a known diagnosis of SpA, will be consented to undertake the MRI scan for research purposes and the MRI scan will be funded by the research grant.

All subjects (cases and controls) will be asked to further consent to provide research samples, including whole blood and stool, for storage and future analysis (serum for biomarker analysis, plasma for proteomic analysis, DNA for genotyping, and stool for microbiome analysis). Collection of

these samples will be funded by the existing research grant, and analysis will be funded by research grants that are currently being applied for.

The control group will receive no further follow up unless clinically indicated. CD subjects in this group with a known history of SpA will be followed up as planned by their primary rheumatology team.

The cases (excluding CD subjects with known SpA who are MRE+ and already under rheumatology review) will be followed up for their second review in the NHS rheumatology SpA clinic approximately 6 months later and will complete the following PROMs; BASDAI, BASFI, VASbp, ASDAS & HAQ-DI. Each patient will also be examined using the BASMI, 68 tender joint count, 66 swollen joint count, the SPARCC enthesitis index, and for skin or nail psoriasis. The following investigations will also be performed as per standard of care if not performed within the preceding month; FBC, renal function, LFTs, CRP and ESR. The patients will also be reviewed in the SpA clinic at an earlier date if indicated for treatment or clinical reasons. However, subjects who already have a diagnosis of SpA and are already under review by a rheumatology team will be followed up as planned by their primary rheumatology team.

Further details of how subjects will be approached, classified as cases or controls, and how the various assessments (clinical, imaging, laboratory) are being funded are detailed in Appendix 1.

1.7 Study timelines & accrual

Study set up:	Up to November 2018
Recruitment and data collection:	December 2018 to February 2020
Analysis and publication of data:	March 2020 to August 2020

Please see Appendix 2 (Schedule of Procedures) and Appendix 3 (Gantt time chart for research timeline).

1.8 End of the study August 2020

2. Introduction

2.1 Background and rationale for the proposed study

Spondyloarthritis (SpA) is a term used to describe a group of chronic inflammatory musculoskeletal diseases that can present with axial and / or peripheral joint disease. SpA encompasses non-radiographic axial spondyloarthritis (nr-axSpA), AS and psoriatic arthritis (PsA). The prevalence of SpA has been estimated to range between 0.01% (Japan) and 2.5% (Alaska and Russia) of the general population [1]. There is an association with the Human Leucocyte Antigen B27 (*HLA-B27*) which is estimated to be present in 50-95% of patients with SpA [2]. Patients with SpA have an excess burden of inflammatory bowel disease (IBD), which primarily includes CD and ulcerative colitis (UC). It is estimated that up to 40% of patients with PsA also have axial disease (PsSpA) [3]. The estimated prevalence of diagnosed IBD in patients with PsSpA is 12% and in patients with AS is 10% [3]. However, few studies have investigated the presence of undiagnosed SpA in patients with IBD. SpA can have a significant negative impact on various aspects of quality of life including employment, social life and sexual relations [4-6]. PsA has been found to be associated with relatively high levels of unemployment (20%–50%) with some improvement following conventional or biologic disease modifying anti-rheumatic drugs (DMARDs) [7, 8]. Timely diagnosis and treatment is therefore potentially crucial.

Novel biologic therapies for SpA have been developed to target the dysregulated innate and adaptive immune systems which underpin its pathophysiological and inflammatory processes. Such targets include pathways involving the cytokines interleukin (IL)-17, IL12/23 and tumour necrosis factor (TNF). These cytokine pathways are also common to the pathophysiological processes of IBD [9-12]. There have subsequently been a number of biological therapies that have emerged over the last decade with a license to treat IBD and SpA, including anti-tumour necrosis factor (anti-TNF), anti-IL-23 and anti-IL 17 agents. Whilst these treatments are not equally efficacious for both conditions, if used appropriately and early in the course of the disease, they can have a significant impact on the burden of disease [13, 14].

Sacroiliitis (inflammation of the sacroiliac joints) is the radiological hallmark of axSpA, but other spinal lesions include spondylitis (inflammation of the vertebral bodies) spondylodiscitis (inflammation of the vertebral discs), enthesitis (inflammation of the spinal ligament insertion points) and the formation of syndesmophytes in chronic disease. Historically, axSpA has been diagnosed using plain radiographs of the sacroiliac joints to assess for sacroiliitis according to the 1984 modified New York criteria for AS [15]. However, over the last 20 to 30 years, cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) has become increasingly utilised. CT scans can better detect chronic bony changes in axSpA, including erosions, sclerosis and ankylosis, compared with radiographs [16-19]. However unlike MRI, they are unable to identify acute inflammatory changes related to bone marrow oedema or chronic changes related to fatty atrophy and MRI is much more effective at detecting early signs of axSpA [16, 20-22]. CT scans also pose higher ionising radiation exposure. MRI does not pose an ionising radiation risk and has therefore been recommended for the assessment of SpA in the 2009 ASAS guidelines [16]. Regarding PsA, this can be diagnosed using the CASPAR criteria [23].

The acute inflammatory changes of axSpA are best seen on MRI using dedicated fluid sensitive sequences such as a fat saturated T2-weighted sequence or a short tau inversion recovery (STIR) sequence. The typical active inflammatory lesions of the sacroiliac joint on MRI include bone marrow oedema, capsulitis, enthesitis and synovitis, and the chronic lesions include sclerosis, erosions and ankylosis [24]. The typical axSpA MRI spinal lesions include spondylitis, spondylodiscitis, enthesitis and syndesmophytes [16].

MRE imaging has been shown to be a useful tool in the diagnosis and assessment of potential complications for patients with CD [25, 26]. The majority of CD patients will have been reviewed by secondary care specialists in gastroenterology, and most will have had cross-sectional imaging in the form of MRE imaging to assess the extent of their CD. These scans also capture the axial (spine and

pelvis) skeleton but radiological assessment of this aspect of the scan is often overlooked and deemed beyond the remit of the initial MRE request. However, these scans contain valuable unreported data, which could be used to screen for the presence of axSpA in patients with CD.

To our knowledge, there have been only 12 studies assessing this in practice; the presence of axSpA features (sacroiliitis) in IBD patients as defined by cross-sectional imaging. Only two of these 12 studies have used MRE imaging for this purpose, with the majority using CT scans, and most of the studies had a small-medium sample size.

Leclerc-Jacob *et al.* (2014) assessed the MRE scans of 186 patients with IBD (131 patients with CD and 55 with UC) and found evidence of sacroiliitis in 16.7% of patients [27]. The incidence of sacroiliitis was found to be equal within the CD and UC group. Gotler *et al.* (2015) had similar findings with 15% of 286 IBD patients having evidence of sacroiliitis on MRE. However, there was no correlation between MRE score and inflammatory back pain [28]. A smaller study by Orchard *et al.* using dedicated MRI images of the sacroiliac joints found sacroiliitis in 17 of 44 (39%) patients with established CD, the majority of which had inflammatory back pain [29]. Bandyopadhyay *et al.* (2015) assessed 120 patients with IBD and found 24 patients (20%) to have sacroiliitis on dedicated MRI of the sacroiliac joints, with 21 of these patients having inflammatory back pain [30]. Chan *et al.* assessed the CT images of 216 patients with IBD compared to 108 controls. They found a significantly higher proportion of sacroiliitis in the IBD patients (15.5 *vs.* 5.6%) [31]. Other studies have found evidence of sacroiliitis on CT scans of patients with IBD ranging from 17% to 68% of the study group [18, 19, 32-36].

Currently, there is limited knowledge on the true prevalence of axSpA in CD patients and there is no reliable screening tool available. Undiagnosed and untreated axSpA can impact significantly on quality of life, but there are a number of potentially effective treatments which could have a significant impact on symptom burden if started in a timely fashion. The development of an effective screening tool for use within the gastroenterology clinic is therefore highly desired by the clinical and research community.

3. Study aim and objectives

3.1 Aim

The aim of this study is to determine the sensitivity and specificity of MRE as a screening tool for axSpA in a cohort of adult patients with CD in a secondary-care hospital, using dedicated axial MRI with clinical assessment as the gold standard.

3.2 Objectives

We hypothesise that existing cross-sectional imaging (MRE) from the routine NHS care of patients with CD can be used to screen patients for evidence of axSpA, thereby prompting onward referral to the rheumatology department for further management.

The objectives of this study are therefore to determine:

1. the validity, sensitivity, specificity and area under the ROC curve of MRE as a screening tool for axSpA in CD, using dedicated axial MRI scans with clinical assessment as the gold standard.

2. the proportion of patients with evidence of axSpA on MRE imaging who fulfill the 2009 ASAS criteria for axSpA, modified New York criteria for AS and the CASPAR criteria for PsA.

3. the proportion of these patients proceeding to non-pharmacological and pharmacological treatment of their axSpA, as a surrogate measure of change in clinical care as a result of MRE screening.

4. the extra-articular features associated with axSpA in CD, in order to better characterise the clinical phenotype of eSpA.

5. whether the site of CD (colon, ileum, *etc*.) predicts the occurrence of axSpA.

4. Study design

4.1 General

The ProSpA-CD study will be divided in to two phases:

1. **The ProSpA-CD-Screen phase:** The review of the patients MRE scan for evidence of axSpA.

2. **The ProSpA-CD-Assess phase:** The clinical assessment of case and control subjects for evidence of axSpA in the clinic setting (including clinical examination, PROMs, blood tests, stool sample testing and a dedicated MRI of the spine) followed by comparison of the two groups.

A prospective single-center observational study will be conducted. For the ProSpA-CD-Screen phase of the study, the gastroenterology team at CUH (Drs Raine and Parkes) will write to approximately 1100 patients with a diagnosis of CD (male and female patients aged 18 years or above) who have had a MRE scan since 2015, asking for their consent to retrospectively review the MRE scans for evidence of axSpA. CD subjects with a known diagnosis of SpA will be eligible and invited to enter the study. Subjects who consent to this will then have their MRE scans reviewed and those with lesions consistent with axSpA (regarded as cases), but who do not have a known diagnosis of SpA, will be referred for further clinical assessment in the NHS rheumatology SpA clinic for evidence of SpA (Dr Jadon's NHS SpA clinic, but assessed by Dr Evans in a supernumerary capacity). At this stage they will also be invited to participate in the ProSpA-CD-Assess phase of the study.

CD subjects with a known diagnosis of SpA who are already under review by rheumatology and who have lesions on MRE consistent with axSpA will be considered as cases and also invited to participate in the ProSpA-CD-Assess phase of the study. However, they will instead be asked to attend the rheumatology SpA research clinic to be assessed for axSpA as this will be considered to be outside of their routine NHS care (Dr Jadon's SpA research clinic, but assessed by Dr Evans in a supernumerary capacity).

CD subjects (including those with a known diagnosis of SpA) who had consented to have their MRE scans reviewed, but do not have evidence of axSpA on MRE will also be invited to participate in the ProSpA-CD-Assess phase of the study as control subjects and will be referred for further clinical assessment in the rheumatology SpA research clinic for evidence of axSpA (Dr Jadon's SpA research clinic, but assessed by Dr Evans in a supernumerary capacity). Cases and controls will be matched for sex and age, with a cases : control ratio of 1:1.

Subjects meeting the inclusion criteria and giving informed consent as per section 5.2.2 will then be recruited in to the ProSpA-CD-Assess phase of the study. Consented subjects will complete the following PROMs; BASDAI, BASFI, VASbp, ASDAS and HAQ-DI [37-40]. Each subject will be examined in the SpA clinic using the BASMI, 68 tender joint count, 66 swollen joint count, the SPARCC enthesitis index, and for skin or nail psoriasis. The following investigations will also be performed *as per* standard of care for the patients with axial skeleton abnormalities on their MRE (MRE+) and no known diagnosis of SpA, if clinically indicated and if not been performed in the preceding month; FBC, renal function, LFTs, CRP, ESR and faecal calprotectin. *HLA-B27* testing will also be requested if not previously performed. These investigations will also be performed for the control subjects and the group of CD subjects with a known diagnosis of SpA who are MRE+ (if not performed in the preceding month and if *HLA-B27* not previously performed) but will be funded by the research grant unless clinically indicated.

A dedicated axial MRI scan of the spine and sacroiliac joints will be performed in all case and control subjects if indicated by the clinical assessment. Subjects in whom a dedicated axial MRI scan is not clinically indicated, or those who have had one performed previously for a known diagnosis of SpA, will be consented to undertake the MRI scan for research purposes and the MRI scan will be funded by the research grant.

All subjects (cases and controls) will be asked to further consent to provide research samples, including whole blood and stool, for storage and future analysis (serum for biomarker analysis, plasma for proteomic analysis, DNA for genotyping, and stool for microbiome analysis). Collection of these samples will be funded by the existing research grant, and analysis will be funded by research grants that are currently being applied for.

The control group will receive no further follow up unless clinically indicated. CD subjects in this group with a known history of SpA will be followed up as planned by their primary rheumatology team.

The cases (excluding CD subjects with known SpA who are MRE+ and already under rheumatology review) will then be followed up for their second review in the NHS rheumatology SpA clinic approximately 6 months later and will complete the following PROMs; BASDAI, BASFI, VASbp, ASDAS & HAQ-DI. Each patient will also be examined using the BASMI, 68 tender joint count, 66 swollen joint count, the SPARCC enthesitis index, and for skin or nail psoriasis. The following investigations will also be performed as per standard of care if not performed within the preceding month; FBC, renal function, LFTs, CRP and ESR. The patients will also be reviewed in the SpA clinic at an earlier date if indicated for treatment or clinical reasons. However, subjects who already have a diagnosis of SpA and are already under review by a rheumatology team will be followed up as planned by their primary rheumatology team.

Please see Appendix 1 for study flow chart, Appendix 2 for schedule of procedures and Appendix 3 for Gantt chart of the research timeline.

4.2 ProSpA-CD-Screen phase

4.2.1 MRE review

The MRE scans at CUH are typically performed using both an oral contrast agent and intravenous Gadolinium to diagnose and assess the extent of CD. The images also capture the lower thoracic spine/ thoracolumbar junction and lumbar spine in the coronal plane and sacroiliac joints in coronal and axial planes. It is the coronal and axial images of the sacroiliac joints that we will be using to assess for evidence of axSpA (sacroiliitis). There are a number of different sequences included for the MRE scans at Addenbrookes hospital including the SSFSE FS (single shot fast spin echo fat suppressed) and LAVA FLEX sequences which are fat suppressed (the complete list of MRE sequences used can be found in Appendix 4).

For the subjects who consented to have their MRE imaging reviewed, two trained scorers (one musculoskeletal radiologist, Dr Elliott Rees; one rheumatologist, Dr Jobie Evans) will assess MRE imaging (sacroiliac joints) for evidence of axSpA using a specifically designed scoring system (see below). The MRE assessors will be blinded to the subjects co-morbidities (other than CD). Training sessions for this will be delivered by a consultant musculoskeletal radiologist (Dr McDonald). This scoring system was developed by an expert musculoskeletal radiologist (Dr McDonald) for this study to specifically identify features of sacroiliitis on both MRE and dedicated MRI spine images, and should permit reliable intergroup comparisons. It has not yet been used in clinical practice due to a lack of previous research on this topic. Scores will be compared and discrepancies decided by consensus. If the two assessors (ER and JE) are unable to reach a consensus for a particular subject, Dr McDonald (considered the 'gold-standard' scorer) will be asked to review and score the images. Dr McDonald will be one of the two expert consultant musculoskeletal radiologists who will be reviewing and scoring the subsequent dedicated axial MRI scans and therefore to prevent any scoring bias, the MRE images reviewed by Dr McDonald in the ProSpA-CD-Screen phase will be anonymised (patient identifiable data removed). The site of CD involvement in the gut will also be reviewed and documented, for further analysis.

Training will also be provided to identify significant sacral fractures and significant infiltrative bone lesions. If an unexpected finding of this sort should arise, the imaging will be reviewed by the

consultant musculoskeletal radiologist (Dr McDonald) and appropriate onward referrals and communication with the patient will be made.

Prior to the commencement of MRE screening, both scorers will score the same ten MREs to determine inter-rater agreement. Both scorers will then score the same ten MREs on two separate occasions a month apart, to determine intra-rater agreement.

The scoring system for sacroiliac joints on MRE imaging will be divided into two sections as follows:

i) Joint margins and contour (score range 0 – 2; 0=normal, 1=mildly abnormal, 2=severely abnormal)
ii) Juxta-articular bone marrow signal (score range 0 – 3; 0=normal, 1=mild, 2=moderate, 3=severe)

4.3 ProSpA-CD-Assess phase

4.3.1 Assessment of patients with lesions on MRE consistent with axSpA (cases)

Patients with lesions on MRE consistent with axSpA (and no known diagnosis of SpA) will be informed by telephone and letter by the gastroenterology team and referred to Dr Jadon's NHS rheumatology SpA clinic. They will also be sent separately an invitation letter, participant information sheet (PIS) and reply slip (study interest form with a stamped-addressed envelope for returns) for the ProSpA-CD-Assess phase of the study by the gastroenterology team. CD subjects with a known diagnosis of SpA who are already under review by rheumatology and who have lesions on MRE consistent with axSpA will also be considered as cases and will be sent an invitation letter, PIS and study interest form. However, they will instead be invited to attend the rheumatology SpA research clinic to be assessed for axSpA (with the control group) as this will be considered to be outside of their routine NHS care.

In the NHS SpA clinic, the patients will be assessed by a single rheumatologist (Dr Evans, in a supernumerary capacity with salary funded by the research grant) for clinical evidence of axSpA *as per* standard of care using the 2009 ASAS criteria for axSpA, modified New York criteria for AS and CASPAR criteria for PsA (see Appendices 5, 6 & 7). The assessment will include a clinical history, examination (including BASMI, 68 tender joint count, 66 swollen joint count, the SPARCC enthesitis index and for skin or nail psoriasis), PROMs (BASDAI, BASFI, VASbp, ASDAS and HAQ-DI), blood samples (FBC, renal function, LFTs, CRP and ESR unless performed in the preceding month, and *HLA-B27* unless previously performed) and stool samples (the monitoring of IBD luminal activity with faecal calprotectin is well established [41, 42]; stool samples will therefore also be collected to measure faecal calprotectin concentrations unless performed in the preceding month). During the consultation, the ProSpA-CD-Assess phase of the study will also be discussed further and patients will be provided with the opportunity to ask any questions they may have regarding the study. If they agree to participate in the study and meet the inclusion criteria, then written informed consent will be taken. The blood and stool tests will be performed as per standard of care if clinically indicated or for research and funded by the research grant if not clinically indicated.

If considered to be clinically indicated as per the above assessments, a dedicated axial MRI scan of the spine and sacroiliac joints will be requested (NHS funded) *as per* standard of care. If considered not to be clinically indicated as per these assessments, consenting subjects will undertake a dedicated axial MRI scan of the spine and sacroiliac joints for research (research grant funded).

As part of the ProSpA-CD-Assess phase of the study, all participants will be asked and consented to have blood (20mls) and stool samples taken for research. These will be stored and undergo analysis at a later date for biomarkers (serum, genotyping, proteomics, microbiome) of axial SpA occurrence and phenotype. Requests for research grants to fund these analyses are currently in progress.

The NHS SpA clinic encounter will be summarised by letter to the patient and copies will also be sent to the patients GP and gastroenterology consultant . The cases (excluding CD subjects with known

SpA who are MRE+ and already under rheumatology review) will then be followed up for their second review in the NHS rheumatology SpA clinic approximately 6 months later and will complete the following PROMs; BASDAI, BASFI, VASbp, ASDAS & HAQ-DI. Each patient will also be examined using the BASMI, 68 tender joint count, 66 swollen joint count, the SPARCC enthesitis index, and for skin or nail psoriasis. The following investigations will also be performed as per standard of care if not performed within the preceding month; FBC, renal function, LFTs, CRP and ESR. The patients will also be reviewed in the SpA clinic at an earlier date if indicated for treatment or clinical reasons.

4.3.2 Assessment of subjects with no lesions on MRE consistent with axSpA (controls)

Subjects (including those with a known diagnosis of SpA) who have consented to having their MRE scans reviewed, but who do not have lesions consistent with axSpA, will be informed in writing of this by the gastroenterology team. They will also be advised that they may be invited to enter the study as a control subject if they are randomly selected through matching (age and sex) to the enrolled 'MRE+ cases' (1:1 ratio). Matched potential control subjects will then be sent an invitation letter, PIS and reply slip (study interest form with a stamped-addressed envelope for returns) by the gastroenterology team to attend the rheumatology SpA research clinic to be assessed by Dr Evans for clinical evidence of axSpA. CD subjects with a known diagnosis of SpA who are already under review by rheumatology and who have lesions on MRE consistent with axSpA will also be invited to attend this clinic for review outside of their routine NHS care but will be considered as cases. Informed consent for study participation in the SpA research clinic will be performed at the start of the consultation. The same clinical assessments, blood and stool samples and dedicated axial MRI scan of the spine and sacroiliac joints will be performed in this control group and in the group of CD subjects with a known diagnosis of SpA who are MRE+ as in the other cases, but will be funded by the research grant unless clinically indicated.

Control subjects in whom there is no evidence of axSpA (by ASAS, modified New York or CASPAR classification criteria) will be informed by letter, which will also be copied to the subjects GP and gastroenterology consultant. Control subjects who do have evidence of axSpA will be informed by letter (also copied to GP and gastroenterology consultant) and asked to return to Dr Jadon's NHS rheumatology SpA clinic for ongoing care. CD subjects who already have a diagnosis of SpA (both in the control group and cases group) and are already under review by a rheumatology team will be informed by letter of the research clinic outcome and will be followed up as planned by their primary rheumatology team. We will also send a copy of the clinic letter to their GP, gastroenterology consultant and named rheumatology consultant to inform them of the clinic findings and to notify them of any outstanding tests/ management plans that may need to be considered at the next clinic review.

4.3.3 Axial MRI Scan

Non-contrast MRI imaging of the whole spine and sacroiliac joints, using a dedicated protocol including T1 weighted and fluid sensitive sequences, will be performed in both the cases and controls. Images will be reviewed by two independent expert musculoskeletal radiologists (Dr McDonald and a colleague musculoskeletal radiologist) and any discrepancies will be decided by consensus agreement. Since MRI review by a second radiologist is not standard of care, it is funded by the research grant for the clinically indicated axial MRI scans. The MRI review by both of the radiologists for the axial MRI scans performed for research purposes is funded by the research grant.

These will be assessed and scored using the spondyloarthritis research consortium of Canada (SPARCC) MRI index criteria which is a validated scoring system for the assessment of spinal and sacroiliac joint inflammation on MRI [43, 44]. To calculate the SPARCC MRI index criteria score for the spine, the six most abnormal discovertebral levels on the STIR sequence are used. At each of the 6 levels, 3 consecutive slices are included and each slice is divided into four quadrants with each quadrant being scored as normal (score 0) or increased signal (score 1). In addition, each slice is scored for intensity and depth of inflammation to give a total possible score of 108 (see Appendix 8). To calculate the SPARCC MRI index criteria score for the sacroiliac joints, six coronal slices of the

sacroiliac joints on the STIR sequence are chosen and each slice is divided in to four quadrants. Each quadrant is then scored as normal (score 0) or increased signal (score 1). In addition, each slice is scored for intensity and depth of inflammation to give a total possible score of 72 (see Appendix 9). The SPARCC MRI index criteria has been validated and reported to be the most reliable MRI inflammation scoring system in a number of studies due to its sensitivity to changes and high inter-reader reliability [45-47]. The dedicated MRI scans will also be scored using the specifically designed scoring system as follows:

i) Joint margins and contour (score range 0 – 2; 0=normal, 1=mildly abnormal, 2= severely abnormal)
ii) Juxta-articular bone marrow signal (0 – 3; 0=normal, 1=mild, 2=moderate, 3=severe)

The SPARCC MRI index criteria score will then be used to determine the validity of our specifically designed scoring system for the dedicated axial MRI scans. The scores of the dedicated MRI scans will then be compared to the MRE scores for each patient to determine the validity of using MRE as a screening tool for axSpA in patients with CD. The sensitivity, specificity and area under the ROC curve of using MRE as a screening tool will also be determined.

If an unexpected finding is identified, such as a fracture or potential malignancy, then the gastroenterology team will be informed and appropriate onward referrals and communication (in-person or telephone, as deemed clinically appropriate) to the patient will be made.

5. Study subject selection

5.1 Eligibility criteria

5.1.1 Inclusion criteria

5.1.1.1 Subjects who are willing and able to give informed consent for participation in the study.

5.1.1.2 Male and female subjects aged 18 years or above.

5.1.1.3 Diagnosed by the gastroenterology team with Crohn's disease (CD).

5.1.1.4 MRE imaging since 2015 for their CD.

5.1.2 Exclusion criteria

5.1.2.1 Subjects unwilling or unable to give informed consent.

5.2 Recruitment, consent and randomisation processes

5.2.1 Recruitment

5.2.1.1 Recruitment for the ProSpA-CD-Screen phase:
The gastroenterology team will write to patients with CD who have had MRE imaging since 2015 (estimated to be approximately 1100 patients) to ask them for consent to review their MRE imaging for evidence of axSpA. CD subjects with a known diagnosis of SpA will be eligible and invited to enter the study. Subjects who consent to this will then have their MRE imaging reviewed by a musculoskeletal radiology specialist registrar (Dr Elliott Rees) and a rheumatology specialist registrar (Dr Jobie Evans).

5.2.1.2 Recruitment for the ProSpA-CD-Assess phase:
Patients with lesions consistent with axSpA on the MRE (and no known diagnosis of SpA) will be informed by telephone and letter by the gastroenterology team and then be referred to Dr Jadon's NHS SpA clinic *as per* standard of care. They will also be invited to enter the ProSpA-CD-Assess phase of the study at that time and consent will be taken during the clinic encounter.

CD subjects with a known diagnosis of SpA who are already under the care of a rheumatology team and have lesions on MRE consistent with axSpA will also be contacted by telephone and letter by the gastroenterology team. However, since they are already receiving standard NHS care for their SpA, they will be sent a separate invitation letter, PIS and reply slip (study interest form) by the gastroenterology team to attend the rheumatology SpA research clinic for assessment of axSpA by Dr Evans outside of their routine NHS care. Informed consent for study participation will be performed at the start of the consultation.

Subjects (including those with a known diagnosis of SpA) who have consented to having their MRE scans reviewed, but who do not have lesions consistent with axSpA on MRE, will be informed in writing of this by the gastroenterology team. They will also be advised that they may be invited to enter this part of the study as a control subject if they are randomly selected through matching (age and sex) to the enrolled 'MRE+ cases' (1:1 ratio). Matched potential control subjects will then be sent an invitation letter, PIS and reply slip (study interest form) by the gastroenterology team to attend the rheumatology SpA research clinic to be assessed by Dr Evans for clinical evidence of axSpA. Any CD subjects with a history of SpA who have been selected as a potential control subject will be sent a separate invitation letter, PIS and reply slip (study interest form) by the gastroenterology team. Informed consent for study participation will be performed at the start of the consultation in the SpA research clinic.

5.2.2 Consent

There will be two separate stages of informed consent.

5.2.2.1 Consent for retrospective review of the MRE scans (ProSpA-CD-Screen phase)

The gastroenterology team will write to all patients with CD and MRE scans since 2015 to ask for consent to review the images for evidence of axSpA. This correspondence will include a PIS and consent form with a stamped-addressed envelope for returns. The pack will also contain a BASDAI questionnaire with six simple questions relating to symptoms of axial inflammatory pain. These six questions, answered on a 1-10 VAS will pose low burden on the subject and be optional to complete, but will markedly help the research team gauge the impact of selection bias on the study given that there may be a preponderance of patients with axial pain willing to participate in the study.

5.2.2.2 Consent to enter the study as a case or control subject (ProSpA-CD-Assess phase)

Patients with lesions on MRE consistent with axSpA (and no known diagnosis of SpA) will be informed of this by the gastroenterology team (by telephone and letter) and be referred to Dr Jadon's NHS SpA clinic for further clinical assessment. Once informed, they will also be invited by post to enter the research element of the study, with an invitation letter, accompanying PIS and reply slip (study interest form) with a stamped-addressed envelope to permit the patient to express if they do or do not wish to participate in the study.

CD subjects with a known diagnosis of SpA who are already under the care of a rheumatology team and have lesions on MRE consistent with axSpA will also be contacted by telephone and letter by the gastroenterology team. The subjects will then be sent a separate invitation letter, PIS and reply slip (study interest form) with a stamped-addressed envelope to permit the subject to express if they do or do not wish to participate further.

Subjects (including those with a known diagnosis of SpA) without evidence of axSpA on MRE will be contacted by the gastroenterology team (by letter) to inform them of the results and will also be advised that they may be invited to enter the study as a control subject. Once the cases have been identified and enrolled, control subjects will then be randomly selected (age and sex-matched in a case : control ratio of 1:1) to enter the research element of the study. The gastroenterology team will then write to these subjects to invite them to enter the study, accompanied by a PIS and a reply slip (study interest form) with a stamped-addressed envelope to permit the subject to express if they do or do not wish to participate further. Any CD subjects with a history of SpA who have been selected as a potential control subject will be sent a separate invitation letter, PIS and reply slip (study interest form) by the gastroenterology team.

During the clinic consultation for both cases and controls, the research study will be discussed further and the subject will be provided with the opportunity to ask any questions they may have regarding the study. If the subject subsequently agrees to take part in the study, then inclusion and exclusion criteria will be assessed and informed written consent will be taken.

6. Study schedule

6.1 MRE Review

Subjects who consent for the ProSpA-CD-Screen phase of the study will have their MRE images reviewed for evidence of axSpA

Subjects who then consent for the ProSpA-CD-Assess phase of the study will immediately undergo the following assessments:

6.2 Clinical questionnaires

BASDAI, BASFI, VASbp, ASDAS & HAQ-DI.

6.3 Clinical assessment and measurements

BASMI, tender and swollen joints, SPARCC enthesitis index, presence of skin and nail psoriasis.

6.4 Blood sampling (total of 40ml)

20ml for standard of care : FBC, LFTs, renal function, CRP and ESR (if not performed within the last one month). *HLA-B27* if not previously performed.

20ml if subjects consent to the research element of the study : for storage and later analysis (serum biomarkers, proteomics and genotyping).

6.5 Stool sample

If subjects consent to the research element of the study, a stool collection kit for faecal calprotectin testing will be provided (if not performed within the last one month) and a further sample will be stored for future microbiome analysis.

6.6 Dedicated axial MRI Scan

This will be requested during the first clinic consultation (cases and controls ; funded by the NHS or research grant as appropriate)

6.7 Definition of the end of study

This will be the date of the last visit of the last participant

If a subject is unable to undertake these assessments immediately, a convenient future research clinic appointment will be made for them and associated travelling costs will be reimbursed.

This study schedule will pose low burden and inconvenience to the subject. Blood sampling will take place at the time of clinical measurements, and are of low total volume (40ml). The subjects will be asked to return to have the dedicated axial MRI scan and to minimise inconvenience, they will be encouraged to return their stool samples when they attend for the scan. Control subjects will be reimbursed for travel and parking costs, and the case subjects will also be reimbursed for any extra travel or parking costs incurred through participating in the study.

Clinical questionnaires are those that would be completed *as per* standard in usual clinical care (except for the control group). However, as we are asking questions in some of the PROMs about the subject's experience of illness, this may cause a degree of upset. Therefore to minimise distress, the clinician (Dr Evans) will talk the subject through each questionnaire prior to completion at the initial clinic visit. In addition, our participation information sheets will stress that participation is voluntary and that the subject can withdraw from the study at any time without their care being affected. Our participation information sheets will also explain the processes taken to maintain anonymity and confidentiality.

The correspondence (invitation letters and PIS) for CD subjects with and without known SpA will have different content to reflect this and to reduce any potential concern or anxiety.

The MRI scan is a non-invasive procedure and the subjects will already have had the experience of having a MRI scan (MRE). However, some subjects may find it difficult to have the MRI scan if they suffer from claustrophobia. Therefore, the MRI scan procedure will be explained to the subject during the initial consultation and they will be provided with the opportunity to ask any questions. We will also emphasise that this is voluntary and that they have the right to decline this or any other part of the study.

7. Data collection, source data and confidentiality

7.1 General

All information collected during the course of the study will be kept strictly confidential.

Each subject will be assigned a unique subject study identification code which will be linked to their hospital number on a secure password protected electronic Microsoft-Access database and stored on the Cambridge University Hospitals NHS Foundation Trust (CUH NHSFT) computer network.

The clinic encounter for the cases in the NHS SpA clinic will be documented on to the CUH NHSFT electronic health record system (Epic) and a letter will be sent out to the patient, their GP and gastroenterology consultant to summarise this encounter. The clinic encounter for the controls and CD subjects with a known diagnosis of SpA in the SpA research clinic will also be documented on the Epic system and a letter will be generated from this clinic to the subject, GP, gastroenterology consultant and rheumatology consultant if appropriate. For the cases in the NHS SpA clinic, the PROMs will be labeled with the patient's details (name, date of birth and hospital number) as this will

be part of their standard NHS care. PROMs for the control group and group of CD subjects with a known diagnosis of SpA in the SpA research clinic will be labeled with the subjects unique study identification code only as this will be outside of their routine NHS care. The blood tests (FBC, renal function, LFTs, CRP, ESR, HLA B27), stool sample for faecal calprotectin and dedicated axial MRI scan of the spine and sacroiliac joints for all subjects within the study will be labeled as per standard trust policy with subject details (name, date of birth, hospital number) and will be requested, reported and stored on the Epic system. Where these tests are performed for research purposes and not standard of care, we will receive written consent from the subject for this. The extra blood and stool samples taken for storage and future analysis for all subjects will be labeled with the unique subject study identification code only. When the subject data is transcribed on to the secure password protected electronic Microsoft-Access database (for all subjects in the study) it will be assigned to the appropriate unique subject study identification code which will be linked to the subject's hospital number. All other identifiable data (such as name, date of birth and NHS ID number) will be removed. This will only be accessible to the investigator team. Michelle Ellerbeck is the 'Data Protection Officer' for CUH NHSFT.

Cambridge University Hospitals NHSFT will comply with all aspects of the Data Protection Act 1998 and operationally this will include:

7.1.1 Consent from subject to record personal details including name, date of birth, address and telephone number, NHS identification number, hospital identification number, GP name and address.

7.1.2 Appropriate storage, restricted access and disposal arrangements for the subjects personal and clinical details.

7.1.3 Consent from subject for access to their medical records by responsible individuals from the research staff, the sponsor or from regulatory authorities, where it is relevant to study participation.

7.1.4. Consent from subject for the data collected for the study to be used to evaluate safety and develop new research.

7.2 Archiving

In line with the principles of Good Clinical Practice and UK Clinical trial Regulations guidelines, at the end of the study, data will be securely archived for a minimum of ten years. Arrangements for confidential destruction will then be made. If a subject withdraws consent for their data to be used, it will be confidentially destroyed immediately.

8. Statistical considerations

8.1 Power analysis

This study will aim to include all CD cases with MRE imaging since 2015; the estimated sample size is therefore 1100 cases.

To our knowledge, there are no studies comparing the sensitivity and / or specificity of MRE scans with gold standard dedicated MRI for the detection of sacroiliitis. However, there have been some studies comparing CT imaging with MRI and these found MRI to be up to 17% more sensitive for the detection of sacroiliitis than CT [48, 49].

Although MRE is expected to be more sensitive at detecting evidence of sacroiliitis than CT, our power calculation is based on the conservative estimate that MRE will detect at ≥60% (sensitivity) of

the cases of sacroiliitis, when compared with the gold standard dedicated axial MRI scan. Therefore with 80% power and a two-tailed alpha of 0.05, it is estimated that ≥60 control subjects (MRE normal) will be required for the study. It estimated that a sample of >60 cases (with abnormal MRE scans) would be needed since the sample size required to assess specificity for a screening test is less than that of sensitivity. Case and controls will be recruited in a ratio of 1:1. From the 1100 MRE scans already performed, it is expected that ≥90% will have a diagnosis of CD, i.e. 990 subjects. We estimate that ≥50% of postally invited participants will consent to participate in the study, giving approximately 445 MRE scans for review.

The two previous studies assessing IBD patients for evidence of sacroiliitis using MRE imaging estimated the prevalence to be 16.7% and 15% [27, 28]. We therefore estimate to recruit ≥66 subjects with positive MRE scans (cases) and ≥66 matched controls. This is a conservative estimate, greater than the minimum number needed to recruit.

8.2 Statistical analysis

Statistical input has been sought from the University of Cambridge Statistics Clinic (PhD student Benajmin Stokell and his supervisor Professor Richard Samworth) and will be supported by Dr Jadon. Inter- and intra-rater reliability testing will be performed for the MRE and axial MRI assessments using intra-class correlation coefficients (ICC). The proportion of CD cases with evidence of axSpA on MRE imaging who fulfil diagnostic criteria for axSpA will be expressed as a percentage. Further descriptive analyses will also be performed on study participants. Due to the possible preponderance of patients with axial pain willing to participate in the study and therefore selection bias, we will not be able to calculate the true prevalence of axSpA in CD patients.

As it is expected that the majority of data collected will be count data with an excess of zero-values, a zero-inflated Poisson (ZIP) regression model will be used to test for association between the presence of axSpA, MRE score, PROMs, clinical indices, site of CD and blood biomarkers. In addition, ZIP regression will be used to test for association between MRE scores and those of dedicated axial MRI scans. Zero-inflated binomial regression will be used as appropriate, where the mean approximates the variance. Two-tailed tests will be performed, and the alpha set at 0.05.

8.3 Missing data

If a subject is uncertain how to complete an outcome measure questionnaire correctly, a research professional will be present to provide support and ensure correct and full completion.

9. Ethical considerations

The study will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000. Informed written consent will be obtained from the patients prior to registration into the study.

Any treatments prescribed for patients within the study who have a diagnosis of axSpA will be in accordance to existing local and clinical commissioning group (CCG) treatment pathways, and will not in any way favour the funder's (MSD) product, namely golimumab (Simponi; an anti-tumour necrosis factor alpha product).

The study will be submitted for approval by the local Research Ethics Committee (REC) via the Integrated Research Application System (IRAS). Ethics approval from the (institutional review board) research and development department of CUH NHSFT will also be sought.

The right of a patient to refuse participation without giving reasons will be respected. The patient will remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

10. Statement of indemnity

Cambridge University Hospitals NHSFT is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Insurance cover is not provided for claims arising from non-negligent harm. Clinical negligence indemnification will rest with the CUH NHSFT under standard NHS arrangements.

11. Safety

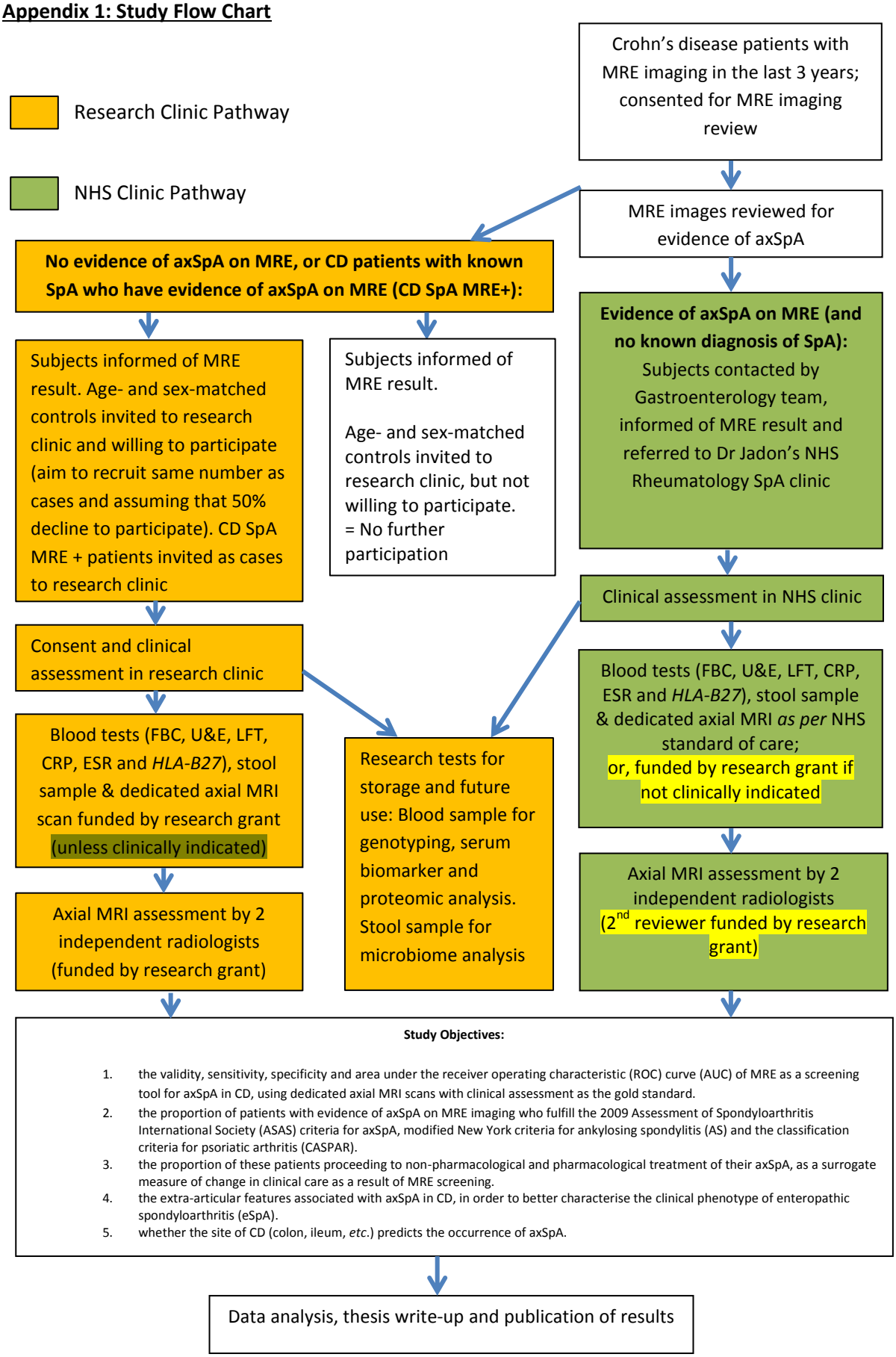
Venepuncture is the only potential risk to patients in this study. The healthcare professionals performing this procedure are trained in venepuncture and will also be able to deal with any potential complications. There are no other significant potential risks from the study procedures.

12. Costings

The study will be funded by MSD (Merck, Sharp and Dohme corporation) who have committed £147,273 for the study. This will fund Dr Evans' salary for the 24 months of the study, research axial MRI scans, research blood tests and stool sampling, consultant radiologist time to review the dedicated axial MRI scans twice, statistical support and office ancillaries.

13. Appendices

Appendix 1: Study Flow Chart



Appendix 2: Schedule of Procedures

Procedure	Timeline / visits			
	Months 0-6	**Months 7-12 (screening/ baseline)**	**Months 13-18 (follow-up)**	**Months 19-24**
Patient consent for MRE image review and recruitment	●			
MRE training and scoring	●			
Systematic literature review	●			
Demographics		●	●	
Medical history		●	●	
Clinical examination		●	●	
PROMs		●	●	
Blood tests *as per* standard of care or research		●	●	
'Research' tests (blood and stool samples)		●		
Faecal calprotectin *as per* standard of care or research		●	●	
Dedicated axial MRI *as per* standard of care or research, with two expert scorers		●		
Statistical analysis			●	●
Write-up of MD thesis and associated papers				●

Appendix 3: Gantt Chart for the Research Timeline

Task	Mar-Nov 2018	Dec 2018-Feb 2019	Mar 2019-Feb 2020	Mar 2020-Aug 2020
1				
2				
3				
4				
5				
6				
7				
8				

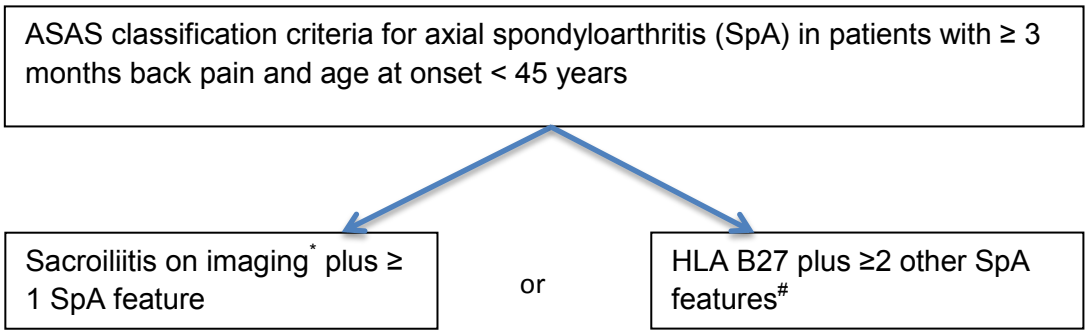
Task:

1. Study setup: Protocol and Ethics approval
2. Systematic literature review (on prevalence of axial spondyloarthritis in patients with Inflammatory Bowel Disease based upon cross-sectional imaging)
3. Magnetic Resonance Enterography (MRE) score training and reliability exercise
4. Patient consent for MRE imaging review and recruitiment (including control group)
5. Scoring of MRE scans
6. Clinical review of patients in spondyloarthritis clinic including completion of patient reported outcome measures and investigations
7. Statistical analyses
8. Thesis and publication of results

Appendix 4: List of sequences for the MRE protocol at Cambridge University Hospitals NHSFT

MRE Sequence	Fat Suppressed
2D CORONAL FIESTA	No
2D AXIAL FIESTA	No
2D CORONAL SLAB MRCP	No
CORONAL SSFSE	No
CORONAL SSFSE FS	Yes
CORONAL DWI B=600	No
CORONAL FIESTA MULTI Dynamic	No
CORONAL 3D LAVA FLEX GAD	Yes
AXIAL 3D LAVA FLEX GAD	Yes

Appendix 5: Assessment of spondyloarthritis international society (ASAS) criteria for classification of axial spondyloarthritis (to be applied in patients with chronic back pain and age at onset of back pain < 45 years) [50].



#SpA Features	*Sacroiliitis on imaging
• Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn's/ Colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP	• Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA • Definite radiographic sacroiliitis according to modified New York criteria

Appendix 6: Modified New York Criteria for the diagnosis of ankylosing spondylitis [15].

Requires radiological criterion & ≥1 clinical criterion

Radiological criterion

Sacroiliitis grade ≥2 bilaterally or grade ≥3 unilaterally

Clinical criterion

1. Inflammatory low back pain & stiffness ≥30m that improves with exercise and is not relieved by rest

2. Reduced motion of the lumbar-spine in both sagittal & frontal planes

3. Limited chest expansion

(having excluded spinal fracture, intervertebral disc disease & fibromyalgia.)

Appendix 7: Classification Criteria for Psoriatic Arthritis (CASPAR) [23].

To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) plus ≥3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.

Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.

† A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.

A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

(The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%)

(† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.)

Appendix 8: The spondyloarthritis research consortium of Canada (SPARCC): Magnetic Resonance Imaging index for scoring inflammation in the spine[43].

SCORING METHODOLOGY

1. All scores are dichotomous – present or absent.

2. After scanning the entire spine, 6 discovertebral levels are selected for scoring. These levels are chosen as representing the 6 most abnormal levels on the STIR sequence. Levels scored at a second time point are the same as those on the first.

3. After selecting levels, three consecutive sagittal slices are chosen for scoring at each level representing the most abnormal slices for that level.

4. Only abnormalities on the STIR sequence are scored. T1 SE images are included for anatomical reference.

5. Bone marrow signal in the centre of each vertebra constitutes the reference normal signal. If the entire vertebra is abnormal, closest normal level is used for reference. Do not score disc lesions.

6. Each discovertebral level is divided into four quadrants: 1 upper anterior endplate, 2 upper posterior endplate, 3 lower anterior endplate, 4 lower posterior endplate. The presence of increased signal in each quadrant is recorded for each of the 3 sagittal slices. Maximum score is 12 per discovertebral level. Maximum score for 6 levels = 72

7. A score for “intense” may be assigned to each level on each slice. High signal from cerebrospinal fluid acts as a reference for assigning an “intense” reading score to a bone lesion. A score of 1 is assigned if “intense” signal is seen in any quadrant on a single slice. Therefore maximum score per slice is 1, per level is 3 and for 6 levels = 18.

8. A score for “deep” may be assigned to each level on each slice. A lesion is graded as “deep” if there is homogeneous and unequivocal increase in signal extending over a depth of at least 1 cm from the surface of the endplate. A score of 1 is assigned if “deep” signal is seen in any quadrant on a single slice. Therefore maximum score per slice is 1, per level is 3 and for 6 levels = 18.

9. Pre- and post-treatment MR images are scored together with observer blinded to time sequence.

Total maximum score is 108:
Presence of “bone marrow oedema” = 72
Presence of “intense oedema” = 18
Presence of “deep oedema” = 18

Appendix 9: The spondyloarthritis research consortium of Canada (SPARCC): Magnetic Resonance Imaging index for scoring inflammation in the sacroiliac joints[44].

SCORING METHODOLOGY

1. All scores are dichotomous – present or absent, 1 or 0.

2. Only 6 coronal slices are assessed. Slices 4-9 are usually selected as those representing the largest proportion of the synovial compartment of the SI joints. Images scored at a second time point are selected to correspond as closely as possible to the first time point – normally 4-9, 3-8 or 5-10.

3. Only abnormalities on the STIR sequence are scored. T1 SE images are included for anatomical reference.

4. Score all lesions within the iliac bone. Within the sacrum, score lesions medially as far as the lateral border of the sacral foramina.

5. Sacral inter-foraminal bone marrow signal is used as the reference for normal to determine a threshold for increased signal in periarticular bone.

6. Each SI joint is divided into four quadrants: 1 upper iliac, 2 lower iliac, 3 upper sacrum, 4 lower sacrum. The presence of increased signal in each quadrant is recorded. Maximum score for two SI joints in each coronal slice is 8. Maximum score for 6 coronal slices = 48.

7. A score for “intense” may be assigned to each SI joint on each slice. High signal from slow flowing venous blood within presacral veins acts as a reference for assigning an “intense” reading score to a bone lesion. A score of 1 is assigned if “intense” signal is seen in any quadrant of an SI joint on a single slice. Maximum score per slice is therefore 2, and for 6 slices = 12.

8. A score for “deep” may be assigned to each SI joint on each slice. A lesion is graded as “deep” if there is homogeneous and unequivocal increase in signal extending over a depth of at least 1 cm from the articular surface. A score of 1 is assigned if “deep” signal is seen in any quadrant of an SI joint on a single slice. Maximum score per slice is therefore 2, and for 6 slices = 12.

9. Pre- and post-treatment MR images are scored together with observer blinded to time sequence.

Total maximum score is 72:
Presence of “bone marrow edema” = 48
Presence of “intense edema” = 12
Presence of “deep edema” = 12

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