Axial Spondyloarthritis in Inflammatory Bowel Disease: Secondary Care Referral Strategies in Norfolk

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Abstract

Background

Axial spondyloarthritis (axSpA) is an inflammatory condition that predominantly affects the axial skeleton, manifesting as chronic back pain (CBP). Referral strategies have focused on expediting suspected axSpA from primary care, but a diagnostic delay remains. Inflammatory bowel disease (IBD) is commonly associated with axSpA. Strategies to identify axSpA in patients with IBD would improve case finding, reduce diagnostic delay, and improve prevalence data for healthcare planning.

Aims

To estimate the frequency of undiagnosed rheumatologist-verified axSpA (RVD-axSpA) diagnosis in IBD patients in the secondary care setting and to demonstrate strategies for their identification in contemporary medical practice.

Methods and Results

In the clinical study, 470 consecutive patients attending gastroenterology clinics were approached. Ninety-one had self-reported CBP >3 months, onset age <45 years, of whom 82 were eligible (gastroenterologist-verified diagnosis, 18–80 years old, biologic therapy naive, no previous diagnosis of axSpA) for assessment. The prevalence of undiagnosed RVD-axSpA is 5% (95% CI 1.3, 12.0). In the imaging study, all abdominopelvic computed tomography (CT) scans for IBD were identified retrospectively from 8 years of imaging archive and limited to 301 (highest diagnostic yield for axSpA: verified IBD diagnosis, 18-55 years old at time of scan). Imaging-compatible changes for axSpA were identified in 60 patients. Of these, 32 responded to participate, and 27 were enrolled. Eight had pre-existing axSpA and 5 denied CBP. The remaining 14 patients underwent assessment, three (21.4%, 95% CI 4.7-50.8) of whom had undiagnosed RVD-axSpA. Therefore, at least 5% (3/60) of patients with IBD who had undergone imaging for non-musculoskeletal indications have undiagnosed RVD-axSpA.

Discussion

This project demonstrated a clinical and imaging strategy which together revealed a significant hidden disease burden of undiagnosed RVD-axSpA among IBD patients and outlines a practical modern pilot framework for referral strategies from gastroenterology and radiology, for IBD patients attending secondary care services.

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To my love^2,

Samantha and Eva.

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Publications

The following publications have resulted from work included in this thesis [1–8]:

Chong Seng Edwin Lim, Raj Sengupta, Karl Gaffney, *The clinical utility of human leucocyte antigen B27 in axial spondyloarthritis*, Rheumatology, Volume 57, Issue 6, June 2018, Pages 959–968, DOI: https://doi.org/10.1093/rheumatology/kex345

Chong Seng Edwin Lim, Mark Tremelling, Louise Hamilton, Alexander Macgregor, Karl Gaffney, *Sat0380 Enhancing Rheumatology Referrals Among Inflammatory Bowel Disease Patients with Suspected Axial Spondyloarthritis*, Annals of the Rheumatic Diseases, Volume 79, June 2020, Pages 1138-1138, DOI: https://doi.org/10.1136/annrheumdis-2020-eular.576

Chong Seng Edwin Lim, Mark Tremelling, Louise Hamilton, Matthew Kim, Alexander Macgregor, Tom Turmezei, Karl Gaffney, *Prevalence of Undiagnosed Axial Spondyloarthritis Among Patients with Inflammatory Bowel Disease: A Secondary Care Cross-Sectional Study*, Arthritis & Rheumatology, Volume 72, Issue S10, October 2020, Abstract Number 1309, DOI: https://acrjournals.onlinelibrary.wiley.com/toc/23265205/2020/72/S10 or https://acrabstracts.org/abstract/prevalence-of-undiagnosed-axial-spondyloarthritis-among-patients-with-inflammatory-bowel-disease-a-secondary-care-cross-sectional-study/

Chong Seng Edwin Lim, Mark Tremelling, Louise Hamilton, Matthew Kim, Alexander Macgregor, Tom Turmezei, Karl Gaffney, *Prevalence of undiagnosed axial spondyloarthritis in inflammatory bowel disease patients with chronic back pain: secondary care cross-sectional study*, Rheumatology, Volume 62, Issue 4, April 2023, Pages 1511–1518, DOI: https://doi.org/10.1093/rheumatology/keac473

Chong Seng Edwin Lim, Samantha Bee Lian Low, Baljeet Dhillon, Shin Azegami, Andoni Paul Toms and Karl Gaffney, *A Service Evaluation of Reporting Standards of Computer Tomography Defined Sacroiliitis Suggestive of Axial Spondyloarthritis in Inflammatory Bowel Disease Patients Imaged for Non-Musculoskeletal Indications*, Arthritis & Rheumatology, Volume 70, Issue S9, September 2018, Abstract Number 691, DOI: https://acrjournals.onlinelibrary.wiley.com/toc/23265205/2018/70/S9 or https://acrabstracts.org/abstract/a-service-evaluation-of-reporting-standards-of-computer-tomography-defined-sacroiliitis-suggestive-of-axial-spondyloarthritis-in-inflammatory-bowel-disease-patients-imaged-for-non-musculoskeletal-indi/

Chong Seng Edwin Lim, Samantha Bee Lian Low, Baljeet Dhillon, Shin Azegami, Andoni Paul Toms and Karl Gaffney, *O34 Is computed tomography defined sacroiliitis suggestive of axial spondyloarthritis reported in patients with inflammatory bowel disease who are imaged for non-musculoskeletal indications?*, Rheumatology, Volume 58, Issue Supplement_3, April 2019, kez105.033, DOI: https://doi.org/10.1093/rheumatology/kez105.033

Chong Seng Edwin Lim, Louise Hamilton, Samantha Bee Lian Low, Andoni Toms, Alexander Macgregor and Karl Gaffney, *Pos0035 One in Twenty Inflammatory Bowel Disease Patients Who Underwent Abdominopelvic Computed Tomography Have Undiagnosed Axial Spondyloarthritis*, Annals of the Rheumatic Diseases, Volume 80, May 2021, Pages 223-223, DOI: https://doi.org/10.1136/annrheumdis-2021-eular.2047

Chong Seng Edwin Lim, Louise Hamilton, Samantha Bee Lian Low, Andoni Toms, Alexander Macgregor and Karl Gaffney, *Identifying Axial Spondyloarthritis in Inflammatory Bowel Disease Patients Utilising Computed Tomography*, The Journal of Rheumatology, Volume 50, Issue 7, July 2023, Pages 895-900, DOI: https://doi.org/10.3899/jrheum.220362

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Acknowledgements

"Everyone has something to contribute to this world. It's just a matter of being given that opportunity to do so." — Grace Hightower. The work in this thesis is my own, but none of it would have been possible without the opportunity given to me by Professor Karl Gaffney. I am grateful for his belief in me and the project. I am also thankful to Professor Alex MacGregor for his support in my MD. The projects were funded by the National Axial Spondyloarthritis Society (national charity), and the Norfolk and Norwich Hospital Charity (local charity), but also AbbVie (industry) through an investigator-initiated study grant.

"No Man Is an Island" — John Donne. I would like to thank all the key individuals who will be mentioned in the statement of contribution below, without which this project would not be possible. However, I would like to thank the unsung individuals that have helped to support the project in the background who are key to the operational aspects of the studies: the NNUH/UEA R&D team: Laura Harper, Emily Woodhouse, Tracy Moulton; the rheumatology admin team: Carol Nolan, Eleanor Sykes, Michelle Bryant, Natalie Smee, Karly Graham; the imaging team: Rebekah Girling, Richard Greenwood, Neil Saunders, Stacey Rosanna, Mary Jane Bennie, Karla Nixson; and the finance team: Julie Mercer, Harriet Block. Special thanks to FMH Postgraduate Research Officer Ly Nguyen for her persistent and caring support in university related admin around the C19 period after the completion of the project without whom the thesis may not have been completed. And of course, Samantha who has been the continual pillar of support that have given me strength and self-belief to push on at the lowest of times.

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Statement of Contribution

The origin of the idea was developed through an iterative process with plenty of discourse between Professor Karl Gaffney and me. I wrote the study grant applications, study protocols and was responsible for obtaining the ethical and NHS R&D approval with the guidance of my supervisors (Professor Gaffney and Professor MacGregor). I was fully involved in the operational aspects including coordination, collecting, and monitoring of both studies. I analysed the data with the assistance of Professor Alex MacGregor, but I am also grateful to Ian Nunney for his support in the initial statistical exploration. Dr Mark Tremelling was instrumental in facilitating access to the IBD cohort and clinical validation. I am indebted to Dr Baljeet Dhillon and Dr Shin Azegami for their assistance in the scoring of CTSI during the service evaluation project, and Dr Matthew Kim in the clinical study for the grading of the MRI scans. The radiology aspects of the study would not have been possible without Professor Andoni Toms, Professor Tom Turmezei and Dr Samantha Low for their coordination and supervision.

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Chapter 1. Introduction

This chapter will explain the terms and background concepts on which this project was built. Firstly, there will be an introduction on axial spondyloarthritis (axSpA), followed by a discussion around the evolution of the concept of axSpA including the importance of early diagnosis and treatment. This precedes a section on a review of imaging in axSpA. Secondly, inflammatory bowel disease (IBD) will be introduced, followed by an examination of the axSpA disease spectrum in patients with IBD whilst also exploring the total and undiagnosed prevalence of axSpA in IBD patients. Next, I will highlight the continued delay in diagnosis in axSpA and outline current referral strategies. Finally, to conclude, there will be a summary of the essential points, also addressing the rationale behind the project.

1.1 Axial spondyloarthritis and inflammatory bowel disease

1.1.1 Axial spondyloarthritis

AxSpA is a chronic inflammatory arthritis predominantly involving the spine and sacroiliac joints, with or without extra-spinal musculoskeletal manifestations (peripheral arthritis, enthesitis, dactylitis) and extra-musculoskeletal manifestations (acute anterior uveitis [AAU], skin psoriasis [PsO] and IBD) [9]. AxSpA has a disease spectrum. This includes non-radiographic axSpA (nr-axSpA) – individuals with axSpA features but without established radiographic changes, and radiographic axSpA (r-axSpA, commonly known as ankylosing spondylitis [AS]) – individuals with axSpA features and radiographic sacroiliitis [10].

AxSpA is diagnosed clinically based on suspicious clinical features supported by laboratory tests (Human Leucocyte Antigen B27 [HLA-B27], raised C-reactive protein [CRP]) and imaging (Magnetic Resonance Imaging [MRI] and/or radiography [X-ray]). MRI enables the identification of typical radiological features of axSpA via the identification of bone marrow changes in a pattern or distribution that is compatible with axSpA in the sacroiliac joints and/or spine, possibly prior to the development of structural changes on X-ray [11–15].

Classification criteria for axSpA (see Figure 1), based on a combination of clinical or imaging features in patients with chronic back pain whose symptoms started before 45 years of age, have been developed by the Assessment of SpondyloArthritis

international Society (ASAS) [16,17]. These are useful for research purposes but are not diagnostic criteria. These classification criteria have often been misapplied as diagnostic criteria leading to difficulties in interpreting the results of some studies [18].

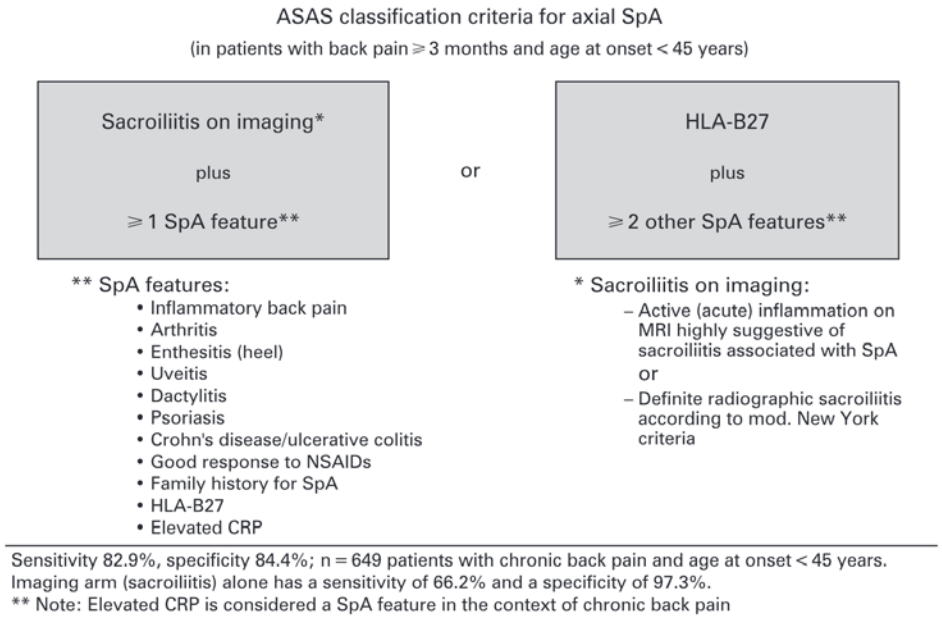

Figure 1: Classification criteria for axSpA by ASAS.

Figure taken from Rudwaleit M, et al. Ann Rheum Dis 2009;68:777–783. Final set of classification criteria for axSpA selected by ASAS. The criteria encompass both patients with and without definite radiographic sacroiliitis. According to the criteria, a patient with chronic back pain (>3 months) and age at onset less than 45 years can be classified in the presence of sacroiliitis (either definite radiographic sacroiliitis or active inflammation of sacroiliac joints on MRI, which is highly suggestive of sacroiliitis associated with SpA) plus at least one typical SpA feature, or in the presence of HLA-B27 plus at least two other SpA features. ASAS: Assessment of SpondyloArthritis international Society; axSpA: axial spondyloarthritis; CRP: C-reactive protein; HLA-B27: human leukocyte antigen B27; NSAID: non-steroidal anti-inflammatory drug; MRI: magnetic resonance imaging; SpA: spondyloarthritis.

1.1.2 Evolution of the concept of axSpA

In the past, clinicians observed a group of chronic inflammatory arthritides that was distinguishable from rheumatoid arthritis. The group consists of AS, enteropathic arthritis or inflammatory bowel disease related arthritis, psoriatic arthritis or skin psoriasis-related arthritis (PsA), reactive arthritis (ReA) or post-infection-related arthritis and undifferentiated peripheral spondyloarthritis. These conditions appeared to have overlapping clinical and radiological features and were given the term "variants of rheumatoid arthritis". Further research showed strong familial associations. As these conditions also tended to be serology negative for rheumatoid factor and displayed strong clinical and radiological associations with either AS or sacroiliitis (inflammation at the sacroiliac joints) as the central feature, the term then evolved to become "seronegative spondyloarthritides". There was intense discourse around the terminologies for this group of conditions but with the subsequent discovery of a strong association of AS with HLA-B27, and subsequent genome-wide association studies with other related conditions, there was a consensus to use the term "spondyloarthritis" to describe this group of conditions. Over the last three decades, with further understanding of these conditions, there has been gradual recognition that these are possible overlapping conditions on a continuum. The conditions have been differentiated based on clinical features, between those who have predominantly axial musculoskeletal manifestations and those with peripheral musculoskeletal manifestations. Recently, with the advances in radiological imaging, axSpA has been further subtyped

into r-axSpA and nr-axSpA as described previously (see Chapter 1.1.1) [19–23].

In today's understanding, the various conditions can be grouped together as spondyloarthritis (SpA). Patients with predominantly axial disease are classified as having axSpA, while those with predominantly peripheral disease are classified as having peripheral SpA (pSpA). Figure 2 below illustrates the group of patients investigated within this thesis – those with both axial musculoskeletal manifestations and inflammatory bowel disease.

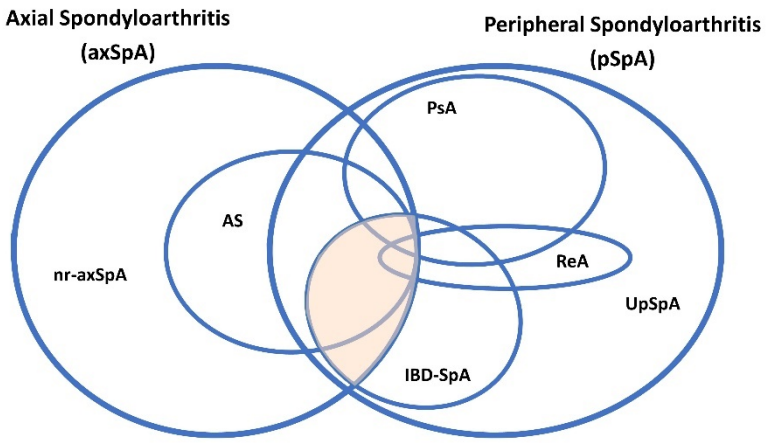

Figure 2: Venn diagram of axial and peripheral spondyloarthritis with respect to previously defined disease entities.

Adapted from Raychaudhuri SP, et al. J Autoimmun 2014 Feb 1;48–49:128–33. AS: ankylosing spondylitis; IBD-SpA: Inflammatory bowel disease related spondyloarthritis; nr-axSpA: non radiographic axial spondyloarthritis; PsA: Psoriatic arthritis; ReA: Reactive arthritis; UpSpA: Undifferentiated peripheral spondyloarthritis.

1.1.3 Concept of early diagnosis and early treatment in axSpA

The symptomatic disease burden appears to be similar in the axSpA spectrum of disease, from nr-axSpA to AS [24]. The axSpA community believes that earlier treatment reduces the progression to irreversible damage (a hypothesis synonymous with the now well-known concept of a "therapeutic treatment window" in the rheumatoid arthritis literature). However, as there is still no robust evidence demonstrating disease regression or termination (i.e. no imaging progression of disease) with treatment, there continues to be an ongoing discourse around the concept of early diagnosis and treatment. Nonetheless, there remains a consensus to early diagnosis and treatment for the control of both symptoms and possible disease progression [25–28].

1.1.4 Imaging in axSpA

Despite previous discussions (See 1.1.1 1.1.1 for more details), the diagnosis of axSpA remains a clinical diagnosis. Radiological imaging has always been an adjunct to diagnosis but over the years, with the improvement of imaging technologies, there has been increasing demand for imaging to provide objective confirmation of pathology and thus improve diagnostic certainty.

In the appropriate context, imaging evidence of inflammation at the sacroiliac joints (sacroiliitis) has been traditionally regarded as the key objective feature in axSpA. In the past, sacroiliitis was only identified from chronic post-inflammatory changes on conventional X-ray (see Figure 3A, Figure 4A, Figure 5A). Most experts would agree that these imaging changes - which usually

consist of radiological features like erosions and joint ankylosis - are all features of longstanding disease and post-inflammatory damage [16,29–31]. These radiographic changes were then included in the classification criteria for AS during the 1980s [32]. While bone damage in axSpA is still best visualised by x-ray imaging - with computed tomography (CT) now gold-standard (see Figures 3B & 3C, Figure 4B & 4C) - developments in MRI technology (see Figure 3D & 3E, Figure 4D & 4E and Figure 5B & 5C) have shown that earlier inflammatory changes can be visualised without the need for ionising radiation [29,31,33,34]. This was incorporated into the ASAS classification criteria for axial spondyloarthritis in 2009 [16] and MRI has been widely used to assist in confirming a diagnosis of axSpA. In recent years there has been increasing awareness of the various imaging differentials which can mimic imaging changes suggestive of axSpA. As the sacroiliac joint abnormalities can vary with age and aetiology, it is important to take the clinical context into consideration [35,36]. In addition, the spectrum of abnormal sacroiliac joint changes in disease can also vary with disease duration and disease phenotype [37–39]. More recently, further research has revealed "similar" imaging features in non-axSpA patients, especially in those who have increased biomechanical stress and strain to the sacroiliac joints e.g. during pregnancy and athletes. Thus, guidance around the acquisition and interpretation of MRI changes has become more formalised [30], to prevent overdiagnosis and over reliance on imaging [37] for the diagnosis of axSpA. With regards to specific imaging in patients with IBD, a recent systematic review looking at the prevalence of axial

spondyloarthritis based solely on cross-sectional imaging compatible sacroiliitis, without confirmation of a clinical diagnosis, concluded that there was much variability and further research was needed [40].

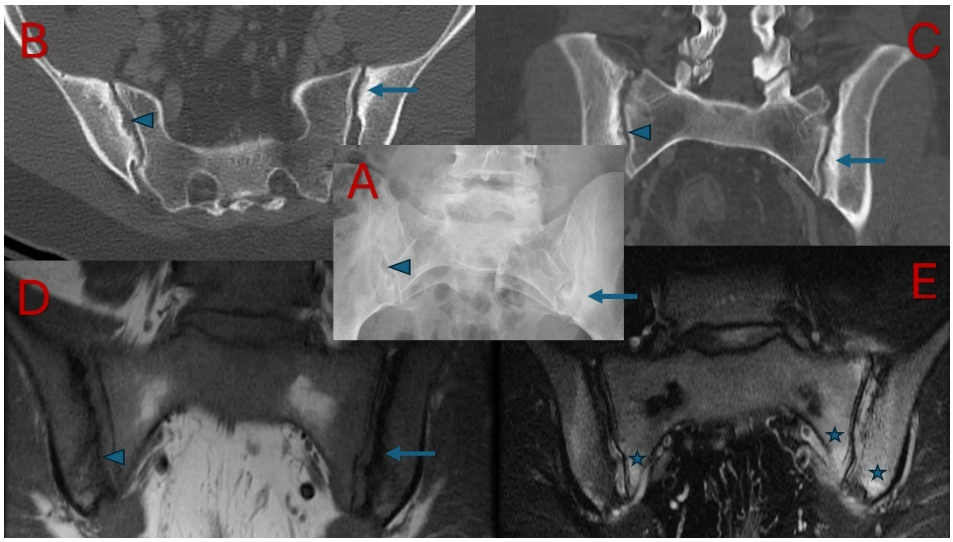

Figure 3: 31-year-old female with bilateral active sacroiliitis.

Figure by author. Pelvic radiograph (A), computed tomographic images in the axial (B) and coronal (C) planes demonstrate bilateral iliac erosions (arrowhead) and subchondral sclerosis (arrow). Magnetic resonance imaging in the T1-weighted (D) and T2-weighted, fat-suppressed (E) sequences demonstrate bilateral iliac erosions, subchondral sclerosis and bilateral osteitis (star, left > right).

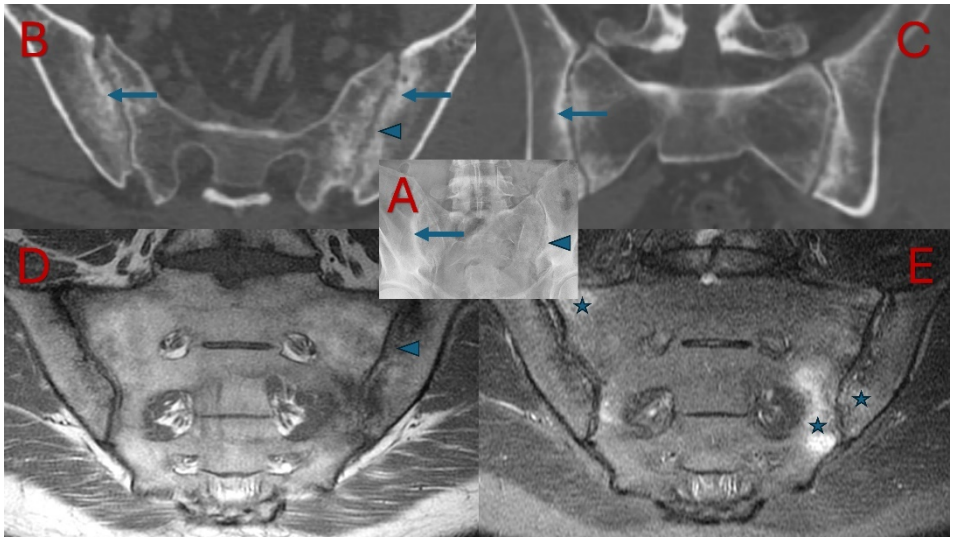

Figure 4: 45-year-old male with bilateral active sacroiliitis.

Figure by author. Pelvic radiograph (A), computed tomographic images in the axial (B) and coronal (C) planes demonstrate bilateral iliac erosions (arrowhead) and subchondral sclerosis (arrow). Magnetic resonance imaging in the T1-weighted (D) and T2-weighted, fat-suppressed (E) sequences demonstrate bilateral iliac erosions, subchondral sclerosis and bilateral osteitis (star, left > right).

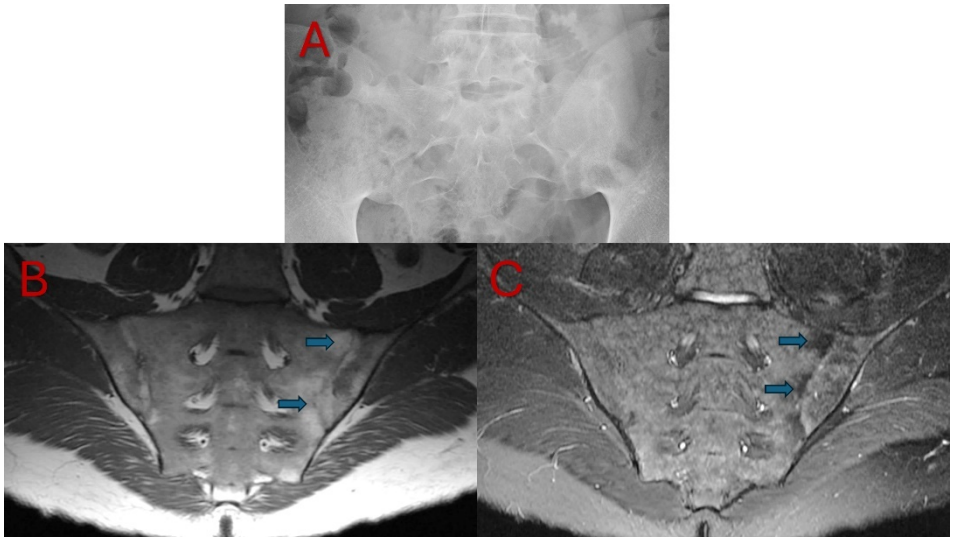

Figure 5: 25-year-old male with bilateral sacroiliac joint ankylosis.

Figure by author. Pelvic radiograph (A), magnetic resonance imaging in the T1-weighted (B) and T2-weighted, fat-suppressed (C) sequences demonstrate bilateral sacroiliac joint ankylosis with left-sided periarticular fat metaplasia (block arrow).

1.1.5 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an overarching term to describe two chronic inflammatory gut disorders. The two major forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD). UC is a chronic inflammatory condition that causes continuous mucosal inflammation of the colon, usually without granulomas on biopsy. It affects the rectum and to a variable extent the colon in a continuous fashion and is characterised by a relapsing and remitting course [41]. CD is a chronic inflammatory condition that causes discontinuous transmural changes anywhere along the alimentary tract, usually with granulomas on biopsy. It affects anywhere from the mouth to anus in a discontinuous fashion and is characterised by a relapsing and remitting course [42]. The diagnosis of IBD is based on clinical evaluation by a gastroenterologist and a combination of endoscopic, histological, radiological, and/or biochemical investigations after exclusion of relevant differential diagnoses [41–43].

1.1.6 AxSpA related IBD spectrum diseases

There is currently no pathognomonic symptom, sign or biomarker that can accurately and precisely diagnose a patient with axial spondyloarthritis or inflammatory bowel disease. Both conditions are still diagnosed clinically. This means that a specialist in rheumatology or gastroenterology clinically assesses an individual, taking into consideration the differential diagnoses, based on the balance of probabilities, organises tests which increase or decrease these probabilities, and then makes a diagnosis based on "best guess". This should not be surprising as this is medicine since the time of Hippocrates [44]. With the advancement of technologies in "diagnostic" testing and computing power to help statistical analysis, the drive towards "evidence-based medicine" is hurtling at an exponential pace, placing laboratory and imaging biomarkers at the forefront of diagnosis, but we must not forget the art of medicine in less well defined conditions like the *axial spondyloarthritis related inflammatory bowel disease* (axSpA-IBD) spectrum diseases. The gold standard as it currently stands is that the diagnosis of axial spondyloarthritis and inflammatory bowel disease is made by clinical diagnosis supported by tests and not the other way around.

In a review in 1992 [45], the authors noted the difficulty in comparing studies due to the different use of case definition. It may not be much different in modern times regarding axSpA-IBD spectrum diseases as studies span the literature between gastroenterology and rheumatology, with each specialty using their best understanding of the other's condition and using a wide range

of disease definitions. For the axSpA spectrum diseases, diagnoses include AS, which is defined using the modified New York Criteria (mNYC), axial SpA using European Spondyloarthropathy Study Group (ESSG) criteria, axSpA using the ASAS criteria, and a physician's clinical diagnosis. For IBD diagnosis, this tends to be consistently based on a gastroenterologist diagnosis (based on Lennard-Jones criteria). Due to this, there is some difficulty trying to define the axSpA spectrum disease in IBD. Nonetheless, the evidence of a connection between axSpA and IBD has been accumulating with time. The following paragraphs will explore these links further.

1.1.6.1 Clinical links

A clear observation can be drawn from the clinical characteristics described in key epidemiological summative studies [46–50]: the presence of two diseases in one individual, the presence of different spondyloarthritis spectrum diseases in one family, the presence of spondyloarthritis spectrum diseases in family clusters, and the prevalence of patients with concomitant conditions being higher than the general population.

1.1.6.2 Biochemical links

Biochemical studies have shown biomarkers which can be found in both AS and IBD patients such as anti-microbial antibodies [anti-saccharomyces cerevisiae (ASCA); perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)] and calprotectin [51–62]. These biomarkers have triggered speculation about the role of a yet unproven gut-spine axis in the pathogenesis of both diseases. A

simplified theory suggests there is a possible susceptibility in gut permeability, leading to chronic local immune responses to gut organisms of varying degrees in both conditions. This leads to microscopic gut inflammation and/or IBD (frank gut inflammation), and through further mechanisms to a distal immune reaction (which may become autonomous) in the spine leading to AS.

1.1.6.3 Genetic links

Genetic studies, historical familial studies, HLA-B27 association studies, and genome-wide association studies (GWAS) hypothesis-free studies have shown an overlap of similar disease polymorphism between AS and IBD. The association of IBD with AS is unlikely to be the result of one condition being causally related to another, but rather based on disease susceptibility genes for one condition predisposing to the other disease [45,63]. As an example, the HLA-B27 gene which is tightly associated with AS at a prevalence of 75–95% in AS patients can also be found in 25–78% of the AS related IBD (AS-IBD) population but remains at background prevalence of 5-14% in IBD patients without evidence of AS [64]. On the other hand, the variants of the CARD15 gene, which encodes the NOD2 protein, increase the risk of Crohn's disease and have been linked to the development of sacroiliitis in IBD patients. Conversely in patients with AS, some variants (R702W, G908R, or 1007fs) appear to confer higher risk for subclinical chronic gut inflammation [65,66].

1.1.6.4 Imaging link

If we assume that sacroiliitis or evidence of inflammation on imaging of the sacroiliac joints are hallmarks of axSpA, then there is evidence from the literature of concomitant AS in IBD patients. McEwen et al showed in 1971 that the radiographic changes in AS and AS-IBD resemble each other closely and constitute a single category [67]. Some of these findings were confirmed by Helliwell et al in 1998 in a similarly designed study [68]. The established bony changes in AS and AS-IBD populations resemble each other and are distinct to the spinal changes in reactive arthritis and psoriatic arthritis [67,68].

1.1.6.5 Ileocolonoscopic studies link

On the assumption that chronic gastrointestinal inflammation on histology from ileocolonoscopic studies are hallmarks of IBD, then there is also evidence from the literature that concomitant IBD occurs in AS patients. A series of ileocolonoscopic studies undertaken in the 1980s in Ghent showed evidence of subclinical (i.e. asymptomatic) gut inflammation in patients with SpA. Frank inflammatory gut lesions (macroscopic; on endoscopy) were found in about 30% of patients with SpA, with 60% exhibiting microscopic histological changes. Most of these lesions were chronic and resembled those of Crohn's disease. The investigators showed that on follow up most of the chronic lesions improved, but in those that persisted, there was also persistence of peripheral articular symptoms. Moreover, in about 20% of patients there was evolution to overt IBD and an apparent association with evolution of

musculoskeletal manifestations into AS [69] (note: here it is possible that the authors, by nature of their broad case definition of seronegative spondyloarthritis at the time of the study, may have inadvertently included cases which today would be classified as pSpA (including ReA and possibly PsA) thereby leading to the observation of more inflammatory bowel lesions in those with peripheral than axial articular involvement). It appears that the presence of peripheral arthritis and the absence of HLA-B27 in those with AS conveys a greater risk of developing IBD [70]. Previously, it was thought that this might be a subclinical form of CD, rather than the prevailing thought now that this possibly reflects the underlying chronic subclinical gut inflammation associated with the AS-IBD spectrum diseases [70]. The Mielants series showed that in SpA, the evolution from non-AS to AS phenotype, or subclinical gut inflammation to IBD phenotype, seems to be related to the persistence and chronicity of initial inflammatory lesions in the gut. IBD or gut inflammation never develops in those patients with normal histology at baseline. They also showed the close relationship between the gut and joint, as clinical remission in joint disease is always correlated with normal gut histology [71–73]. In my interpretation, the Mielants studies, especially those comparing non-AS and AS groups, may be interpreted to suggest that the evolution to AS-IBD is not absolute. In their AS sub-cohort, there were cases without subclinical gut inflammation which may suggest that in patients who have more AS genetic load e.g. more likely to be HLA-B27 positive with early onset of AS phenotype, there is a tendency to have only intermittent

bowel changes at the start of their disease and subsequently have no further evolution of bowel problem, despite a progressive musculoskeletal phenotype. On the other hand, there are those in their sample with a non-AS predominant phenotype and chronic bowel inflammation. This may represent a middle ground, where patients have both sets of genetic load and eventually express both phenotypes but to a milder extent. Finally, there are those with an AS phenotype who also have persistent chronic gut inflammation. These may represent patients who have susceptible IBD genetics that predispose them to eventually progress to IBD with time (they tend to be HLA-B27 negative).

1.1.6.6 Therapeutic link

The use of modern-day targeted therapeutics has allowed the scientific community to learn more about the links between the two diseases using therapeutics as a biological scalpel. Previous non-biologic trials in axSpA have shown mixed results, with a tendency for better responses in those with peripheral arthritis. Axial symptoms appeared to be independent of bowel disease, and the prevailing perception twenty years ago was that treatment should primarily target bowel disease in those with both conditions [69]. Modern clinical trials have now shown that there may be common inflammatory pathways (with Tumour Necrosis Factor [TNF] inhibitors and Janus kinase [JAK] inhibitors proving effective in both diseases). However, trials have also shown that there may be end organ or tissue-specific inflammatory pathways for those clinical phenotypes at the chronic end of the axSpA-IBD spectrum diseases. In established IBD and AS, there is a differential response to targeted therapeutics, for example the targeting of IL-23 versus IL-17 works for one disease but not the other. In my view, it may ultimately be the burden of susceptible genetic load which determines the positioning of one's disease phenotype on the axSpA-IBD disease axis e.g. 1. frank IBD with or without symptomatic sacroiliitis, 2. subclinical gut inflammation with axial inflammatory arthritis with or without peripheral arthritis or 3. frank AS with or without subclinical gut inflammation, and thus resulting in variable responses to targeted biological treatments [74–82].

1.1.6.7 Summary

The understanding of a connection between AS and IBD has grown from early clinical observations in familial studies, traditional genetics studies and epidemiological studies, through advances in genome-wide association studies, and the use of therapeutics as a molecular scalpel. Imaging and ileocolonoscopic studies have afforded the opportunity to visualise objective inflammation. There is now improved understanding of these connections and hence different hypotheses on the pathogenesis of both conditions are being debated, including the possible presence of a spectrum or continuum between axSpA and IBD (see Figure 6).

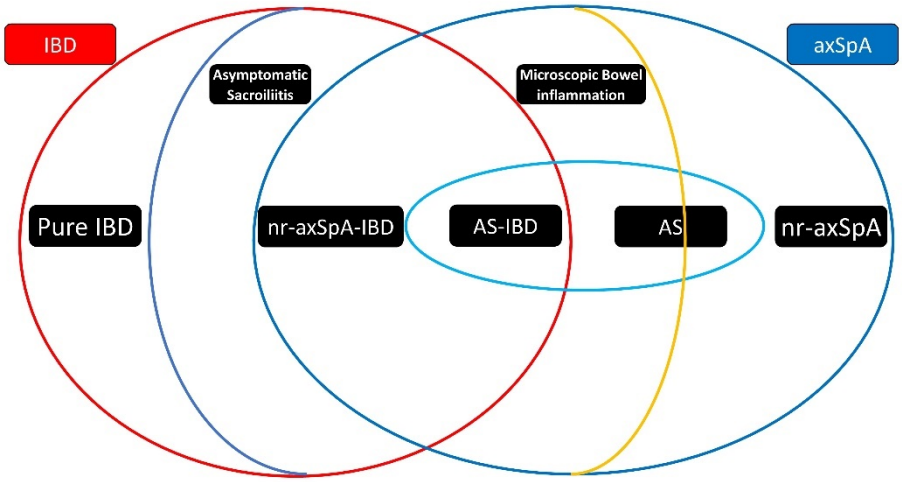

Figure 6: Venn diagram of axial spondyloarthritis spectrum diseases in inflammatory bowel disease.

Figure by author. AS: ankylosing spondylitis; AS-IBD: ankylosing spondylitis related inflammatory bowel disease; IBD: inflammatory bowel disease; nr-axSpA-IBD: non-radiographic axial spondyloarthritis related inflammatory bowel disease; nr-axSpA: non-radiographic axial spondyloarthritis.

1.2 Prevalence of AxSpA in IBD

1.2.1 Total prevalence

There are many previous studies estimating the total prevalence of axSpA spectrum of diseases in IBD patients including a few systematic reviews. The estimated range of prevalence of patients having a diagnosis of AS in IBD patients is between 1% to 25% [64,65,83,84], with a recent calculated pooled prevalence of 3% [50]. For axSpA diagnosis in IBD patients, the prevalence range varies considerably and is reported to be between 4% and 7% [46,49]. Sacroiliitis identified using cross-sectional imaging (symptomatic and asymptomatic) is common, with a prevalence in IBD patients ranging from 2.2% to 68% [40,64,65,83,84], and a recent calculated pooled prevalence of 10% to 21% [40,50].

1.2.2 Undiagnosed prevalence

Contemporary evidence of prevalence of undiagnosed axSpA is sparse. Few studies have explored the burden of undiagnosed axSpA in the IBD population as their main study outcome. Previous studies included in a recent systematic review showed that most cross-sectional prevalence studies either collected their data retrospectively or if collected prospectively, the proportion of undiagnosed patients was not specified. It also highlights the absence of adequate contemporary studies that reflect the current population and practice [50,85–87].

1.3 Continued delay in diagnosis

AxSpA typically begins in the second and third decades [88]. Delay to diagnosis is a major problem with a pooled mean delay of about 7 years in a recent systemic review and meta-analysis [89]. This means that patients often endure intolerable symptoms, and suffer worse outcomes (disease activity, function, radiographic), despite the availability of effective new therapies [90]. Early treatment offers the best chance of drug-free remission and early disease responds best to Tumour Necrosis Factor inhibitors (TNFi) [91,92].

Sykes et al [93] have recently shown that the delay to diagnosis has not improved despite advances in modern imaging and new approaches to diagnosis. They divided 1193 patients with a physician-verified diagnosis of axSpA into a historical (diagnosed pre-2009) and current cohort (diagnosed 2009-2013) and found that the average delay to diagnosis in the historical cohort was 8.53 years, and 9.39 years in the current cohort. They concluded that there is still a need for further targeted education of health-care professionals to address the issue of delay to diagnosis. The National Axial Spondyloarthritis Society (NASS), the only charity in the United Kingdom dedicated to supporting patients with axSpA, also concluded in a recent conducted survey of axSpA patients that the average delay to diagnosis (onset of symptoms to diagnosis) is still 8.50 years [94].

1.4 Referral strategies

Despite advances in imaging and improving understanding of the disease, the early diagnosis of axSpA remains challenging. This is likely to be one of the reasons contributing to the long delay to diagnosis and poor long-term outcomes. The international rheumatology community has been investigating different referral strategies to identify undiagnosed cases of axSpA [95].

1.4.1 Patients with lower back pain

Chronic lower back pain (CBP) is usually the main presenting clinical symptom of axSpA; thus, it is the natural starting point for research into referral strategies in primary care. However, adding to the difficulty in identifying the right patient group for referral, we also need to appreciate that lower back pain of an inflammatory nature is not easy to identify despite the multiple proposed definitions of inflammatory back pain (IBP) [96]. Also, lower back pain can present with biomechanical or degenerative characteristics leading to confusion [96,97].

Referral strategy trials have been proposed to facilitate identification of axSpA but almost all are primary care referral strategies based on a combination of inflammatory back pain, imaging findings, HLA-B27 results and associated clinical features [12,98,99]. A single "best" strategy seemed elusive until recently when a European group found, after comparing thirteen referral strategies, that a composite features referral tool appears to be the best way of identifying suspected early SpA patients for assessment in secondary care [95].

1.4.2 Patients with extra-musculoskeletal manifestations

Besides back and musculoskeletal discomfort, extra-musculoskeletal manifestations (EMM) including inflammatory conditions of the eye, bowel and skin such as AAU, IBD and PsO are common among patients with axSpA.

To address the problem of delay to diagnosis, NASS has developed the "BACK PAIN PLUS" campaign which is an awareness campaign targeted at secondary care specialists who manage patients with common EMM of axSpA. NASS proposes that these patients should be screened for the presence of chronic back pain (with inflammatory features) and referred to rheumatology if they are found to screen positive [100]. This guidance has also been echoed in the guidelines of the ASAS-endorsed recommendation for the early referral of patients with suspected axial spondyloarthritis [101].

In patients presenting with PsO, there have been multiple referral tools and strategies previously published [102,103]. It is likely that the phenotype of psoriatic spondyloarthropathy, with visible peripheral joint and skin disease, makes disease identification more straightforward. [104–106].

In patients with AAU, Haroon et al and Sykes et al have recently developed algorithms to direct patients with an acute presentation of inflammatory eye disease to rheumatology [107,108].

In IBD patients, questionnaires have been developed to identify spondyloarthritis, using the ASAS classification criteria [109–112]. However, there has been no attempt to develop a clinical referral

strategy in IBD. As patients with IBD often undergo imaging to evaluate the presence, extent, and severity of their gastrointestinal disease, an incidental finding of sacroiliitis could be the trigger for a more comprehensive assessment aimed at diagnosing axSpA. Recent evidence has shown that the prevalence of sacroiliitis on CT performed in patients with IBD for non-musculoskeletal (non-MSK) indications ranges from 2.2% to 25% [113–116]. In parallel, a practical CT screening tool has been developed to differentiate sacroiliitis in (i) patients with axSpA versus controls [117] and (ii) patients with IBD versus controls [116], therefore this could potentially be used to identify axSpA in IBD patients.

It is good practice and should be routine practice that symptomatic IBD patients with incidental Computed Tomography-defined Sacroiliitis (CTSI) suspicious of axSpA should be referred to rheumatology for a clinical assessment (including an MRI scan in the modern diagnostic workup of axSpA) to verify the diagnosis of axSpA. However, there is evidence that this is not being undertaken [112,116].

1.5 Outline and Rationale of Project

To recap, axSpA is known to be closely associated with IBD. The spectrum of axSpA includes patients with nr-axSpA and r-axSpA (formerly known as AS). Due to evolving case definitions of axSpA and differing methodologies used to identify cases, the reported prevalence of axSpA diagnosis in IBD patients varies widely between studies. The pooled prevalence of AS diagnosis in IBD patients has been estimated at 3% [50], whereas the estimated prevalence of axSpA diagnosis in IBD patients is reported to be 7.7% [118]. Evidence for the contemporary prevalence of undiagnosed axSpA in IBD patients is sparse [85–87]

AxSpA is a physician-verified diagnosis rather than one based on the fulfilment of contemporary classification criteria. Despite advances in imaging technology, improved understanding of the axSpA concept and awareness campaigns [14,17,119], delay to diagnosis is still a major problem with an average delay of 7–10 years. Patients often endure intolerable symptoms and worse outcomes (disease activity, function, radiographic), despite the availability of effective new therapies [90,94].

Primary care referral strategies have been extensively researched over the years to identify the cohort of patients presenting with lower back pain which should be referred for rheumatology assessment [95]. As extra-musculoskeletal manifestations are also common among patients with axSpA, there is evolving research into secondary care referral strategies, and strategies for patients presenting with AAU have been published. [12,107,120]. Although

questionnaires have been developed to identify the entire spectrum of SpA among patients with IBD, these used the ASAS classification criteria and were not based on a rheumatologist diagnosis [109–112].

To date, there are no published evidence-based clinical referral strategies to identify concurrent clinically undiagnosed axSpA in patients with IBD, reflecting a gap in knowledge. However, before we can proceed to develop axSpA clinical referral strategies specific for IBD patients, as has been done in the primary care chronic back pain population and in patients presenting with AAU [12,107], there is a need to quantify the 'hidden burden' or undiagnosed prevalence of axSpA in IBD patients in current daily clinic practice. In addition, there are no published imaging referral strategies for patients with IBD. There are also no studies reporting the proportion of IBD patients with CT imaging changes compatible with axSpA, who have subsequently been diagnosed with axSpA by a rheumatologist, defined here as a *rheumatologist-verified diagnosis of axial spondyloarthritis* (RVD-axSpA).

The research questions above (and the project's aims and objectives outlined in Chapter 2) are addressed by two studies labelled under the umbrella N-ASPIRE (Norfolk - Axial SPa Ibd REferral). The first is a clinical strategy study named *N-ASPIRE Clinical Strategy Study* which will be described further in Chapter 3. The second is an imaging strategy study named *N-ASPIRE Imaging Strategy Study* which will be described further in Chapter 4.

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Chapter 2. Aims and Objectives

2.1 Aims of the project

The principal aims are to estimate the frequency of undiagnosed axSpA diagnosis in IBD patients in the secondary care setting and to demonstrate strategies for their identification in contemporary medical practice.

2.2 Objectives of the project

- To estimate the prevalence of undiagnosed axSpA in routine secondary care IBD patient population.
- To estimate the prevalence of undiagnosed axSpA in IBD patients with CTSI when being investigated with CT scans for non-MSK reasons.
- To demonstrate that there are undiagnosed axSpA cases through a clinical strategy.
- To demonstrate that there are undiagnosed axSpA cases through an imaging strategy.
- To explore if the utility of a validated CT screening tool can facilitate the identification of undiagnosed axSpA in symptomatic CTSI patients.

The aim of the N-ASPIRE Clinical Strategy Study is to estimate the prevalence of RVD-axSpA in the IBD population (with the aid of contemporary imaging technologies such as MRI) as the undiagnosed cases may represent a "hidden burden" of axSpA. I hope to demonstrate a feasible clinical strategy and framework which future studies can use to design an evidence-based referral tool, to improve the identification of axSpA in IBD patients in the Norfolk population.

The aim of the N-ASPIRE Imaging Strategy Study is to understand the proportion of people who may have a diagnosis of axSpA in the IBD population and have imaging-compatible changes in pre-existing imaging done for non-MSK indications. The undiagnosed cases may represent a further "hidden burden" of axSpA in IBD patients. The study will also explore the utility of a known screening tool [117] as an adjunct to help improve imaging interpretation and the onward management of these patients. This may be an additional strategy to identify undiagnosed axSpA in the IBD population by utilising pre-existing scans which have been undertaken for non-MSK indications in IBD patients with the highest diagnostic probability of having axSpA.

This is in line with recent research recommendations from the National Institute for Health and Care Excellence (NICE) guidance NG65 on axSpA, calling for evidence based IBD-specific strategies [121]. This approach may reduce overall healthcare utilisation costs, reduce delay to diagnosis, and facilitate access to available effective treatments.

Chapter 3. N-ASPIRE Clinical Strategy Study

3.1 Introduction

This chapter describes the clinical referral strategy through the design of the N-ASPIRE Clinical Strategy Study. The study also estimated the prevalence of the undiagnosed rheumatology-verified axSpA diagnosis in an IBD population who is attending routine secondary care - the "Hidden Burden" of disease.

3.2 Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee East of England – Cambridgeshire and Hertfordshire Research Ethics Committee (223356 18/EE/0102). All participants gave written informed consent before study inclusion.

3.2.1 Study design and setting

This was an observational cross-sectional study. Screening questionnaires (SQ) were sent prospectively to consecutive patients attending routine IBD clinics between September 2017 and February 2019 at a large university teaching hospital serving approximately 3000 IBD patients. Following this, a structured clinical assessment of a subset of participants (including those with and without chronic back pain) was conducted to determine the proportion with undiagnosed RVD-axSpA (see Figure 7).

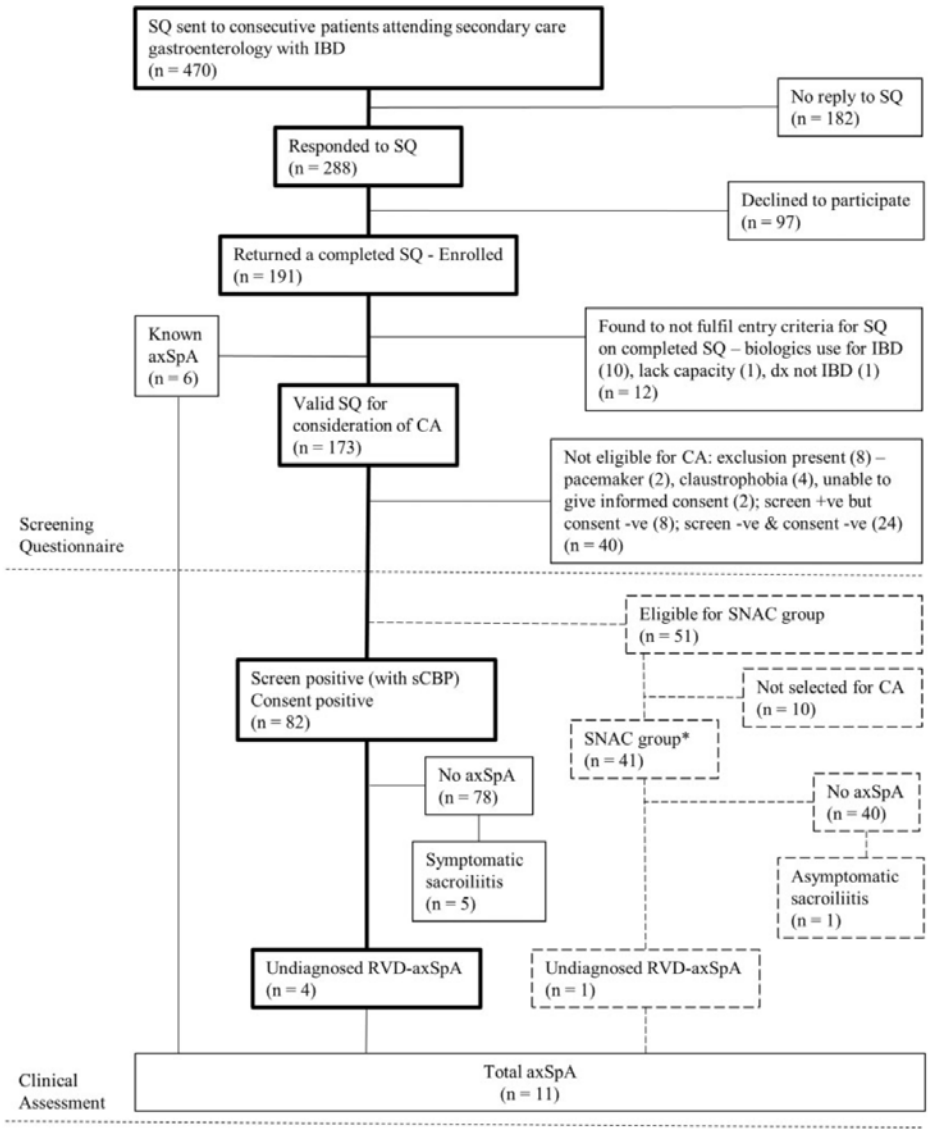

Figure 7: Flow chart of N-ASPIRE Clinical Strategy Study.

*Figure by author. *Only 40/41 MRI scan had full protocol acquisition. +ve: positive; –ve: negative; axSpA: axial spondyloarthritis; dx: diagnosis; CA: clinical assessment; RVD: rheumatologist verified diagnosis; sCBP: self-reported chronic back pain >3 months, age onset <45 years old; SNAC: Screen Negative Assessment Control; SQ: screening questionnaire.*

3.2.2 *Study population*

Patients fulfilling the eligibility criteria (gastroenterologist verified diagnosis, age range 18–80 years old, biologic therapy naive, no previous diagnosis of axSpA); and a moderate diagnostic probability of axSpA defined as self-reported chronic back pain >3 months and onset age <45 years were invited for rheumatology assessment. Patients on biologics unlike other IBD treatments were excluded because inflammatory lesions may be suppressed and could interfere with objective assessment and diagnostic assignment. Patients with pre-existing confirmed axSpA were verified from their medical records and contacted via telephone to collect clinical characteristics but were not reassessed.

3.2.3 *Screening questionnaire*

This was a self-reported questionnaire [122] (see Appendix 1. Protocol of the N-ASPIRE Clinical Strategy Study) which enquired about the presence of a previous axSpA diagnosis, presence of back pain lasting >3 months, age of onset of back pain, nature of back pain, personal and family history of associated axSpA conditions, and brief description of their inflammatory bowel disease and treatment.

3.2.4 Clinical assessment

This included a medical review, physical examination [including joint and tender point count, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [123], dactylitis count, Bath AS Metrology Index (BASMI) [124]], patient-reported outcomes [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [125], Bath Ankylosing Spondylitis Functional Index (BASFI) [126], Bath Ankylosing Spondylitis Patient Global Score (BASG) [127], Harvey–Bradshaw Index [128], Partial Mayo Index [129])], laboratory tests (CRP, ESR, HLA-B27), pelvic X-ray, axSpA protocol MRI of sacroiliac joints and spine [30], and remote review by a panel of axSpA rheumatologists.

The Harvey–Bradshaw Index is a simple, non-invasive clinical tool based on symptoms and clinical findings that is used to assess the severity of CD. It helps to monitor the progression or remission of disease and guide treatment decisions. The Partial Mayo Index is a simplified version of the Mayo Clinic Score, that relies on clinical and patient-reported data to assess the severity of UC. It allows the evaluation of disease activity with fewer components, making it easier to use in clinical practice for monitoring and treatment decisions.

3.2.5 Interpretation of results

The pelvic X-ray and MRI of the sacroiliac joints and spine were performed as per the local axSpA protocol, read and reported by the musculoskeletal radiology team according to routine clinical practice. Any imaging discrepancies were discussed at a weekly

radiology multidisciplinary meeting and agreement made by a consensus majority. Furthermore, grading of radiographic sacroiliitis was undertaken by two radiology colleagues with reference to the modified New York criteria [32]. A positive sacroiliac joint MRI for inflammation was determined with reference to the ASAS-OMERACT 2009 definition [15] incorporating recently updated guidance [14]. A positive spinal MRI for inflammation was made with reference to the ASAS-OMERACT 2012 definition [130]. Both imaging modalities were assessed independently from one another.

3.2.6 Rheumatologist-verified diagnosis of axSpA (RVD-axSpA)

Each subject was discussed in a virtual meeting: an initial discussion solely based on clinical history and examination findings, and a second following the availability of laboratory and imaging results. The panel comprised of three rheumatologists with a specialist interest in axSpA. Each made either a positive or negative diagnosis of axSpA. They also indicated their level of diagnostic confidence on a 10-point Likert scale. RVD-axSpA was confirmed when at least two of the three rheumatologists agreed. The level of confidence (LoC) was reflected by an average of the three Likert scales. A similar process was undertaken when the results of imaging and laboratory results were available. Any discrepancy between the pre- and post-investigation diagnosis was discussed in a further summary meeting, and a final diagnosis made by a majority consensus vote after a subsequent review of all clinical, laboratory and imaging information.

3.2.7 Power calculation and statistical analysis

It was estimated that 73 patients were needed to detect a minimum axSpA prevalence of 5% at a nominal threshold significance of P = 0.05. Based on the assumption that 50% would respond to the SQ, and 50% of the respondents [131–133] would have self-reported CBP (sCBP) of whom 75% would take up an invitation for clinical review, the study aimed to screen an initial sample of 390 consecutive IBD patients. Descriptive statistics were used for patient characteristics. Inter-clinician diagnostic agreements were calculated using the kappa statistic with estimated confidence intervals. Descriptive statistics were used to present the average LoC. For calculation of prevalence, the frequency of cases (i.e. RVD-axSpA) to the base population (i.e. IBD patients who returned a valid SQ with sCBP and were clinically assessed) was used with a calculated confidence interval when appropriate. Data analysis was performed using STATA Version 15 (StataCorp, TX, USA) and Microsoft Excel 2016 (Microsoft, WA, USA).

3.2.8 Screen negative assessment control (SNAC) group

A sample of consecutively enrolled IBD patient without self-reported CBP (>3 months and onset age <45 years) were selected (for every two screen-positive patients assessed, matched as closely to gender and age as possible) and assessed as per the above clinical assessment (except pelvic X-ray due to ethical reasons) (see Figure 7).

3.3 Results

3.3.1 Main patient characteristics

In total, 470 consecutive IBD patients were approached; 288 (61%) expressed interest, and 191 (66%) returned a completed SQ of which 173 were valid (see Figure 7, which also lists the number of patients with known axSpA). Ninety-one (53%) had self-reported CBP >3 months, onset age <45 years, of whom 82 (90%) were eligible for clinical assessment (see Figure 7, which also lists reasons for exclusion). Their detailed clinical characteristics are shown in Table 1-3 and Table 4-5 .

The salient clinical characteristics of those assessed in the clinical assessment are as follows. The mean age was 52 years, 37% were male, 74% had ulcerative colitis, 26% Crohn's disease and 66% were in remission. The prevalence of inflammatory back pain was 38%, 35% and 29% fulfilling Calin[134], Berlin [135] and ASAS expert's IBP criteria [136], respectively. The frequency of acute anterior uveitis, psoriasis and other inflammatory peripheral musculoskeletal manifestations (i.e., arthritis, enthesitis, dactylitis) were reported to be 5%, 7% and 16%, respectively. Twenty-nine (35%) patients had a family history of axSpA-related disorders (of which 62% IBD, 52% skin psoriasis, 4% axSpA). Mean CRP (reference range: 0–10) and erythrocyte sedimentation rate (ESR; reference range: 0–20) were 4.3 mg/l and 14 mm/h, respectively; 7% were HLA-B27 positive; 4% fulfilled the ASAS definition of a positive MRI and 6% fulfilled the radiological criteria of the mNYC. With respect to the four patients with RVD-axSpA and self-

reported CBP, three were HLA-B27 positive; there was an average of two relevant ASAS axSpA features; one fulfilled the ASAS definition of a positive MRI; and two fulfilled the radiological criteria of the mNYC.

Patient Characteristics[a]	Eligible patients who attended the clinical assessment visit (n=82)
Demographics and social habits	
Age at invitation: years, mean (S.D.)	51.9 (15.0)
Gender: male, n (%)	30 (36.6)
Ever smokers, n (%)	49 (60.0)
Characteristics of chronic back pain	
CBP: yes, n (%)	82 (100.0)
Age of onset of back pain, mean (S.D.)	27.0 (9.2)
Rheumatologist's IBP[b], n (%)	16 (19.5)
Presence of inflammatory back pain via classification criteria	-
IBP Calin, n (%)	31 (37.8)
IBP Berlin, n (%)	29 (35.4)
IBP ASAS, n (%)	24 (29.3)
Other relevant axSpA history	
Positive personal history of SpA conditions, n (%)	21 (25.6)
Acute Anterior Uveitis, n (%)	4 (4.9)
Skin psoriasis, n (%)	6 (7.3)
Inflammatory peripheral MSK conditions (arthritis, enthesitis, dactylitis): yes, n (%)	13 (15.9)
Non-inflammatory peripheral MSK condition, n (%)	63 (76.8)
Positive family history of SpA conditions, n (%)	29 (35.4)

Table 1: General and axSpA characteristics of participants who attended the clinical assessment visit of the Clinical Strategy Study (part 1).

Type of positive family history of SpA conditions	-
IBD, n (%)	18 (62.1)[d]
Skin psoriasis, n (%)	15 (51.7)[d]
AS or axSpA, n (%)	1 (3.5)[d]
Acute Anterior Uveitis, n (%)	0 (0.0)[d]
Reactive arthritis, n (%)	0 (0.0)[d]
Number of other co-morbidities[c]	-
count, mean (S.D.)	2.1 (2.1)
count, median (IQR)	2 (3)
Current use of NSAIDs for MSK symptoms, n (%)	16 (19.5)
MSK symptoms improved with NSAIDs, n (%)	14 (87.5)[d]
Examination, rheumatological measurements and PROMs	
BMI: kg/m2, median (IQR)	27.4 (7.2)
Swollen joint count: max 44, median (IQR)	0.0 (0)
Tender joint count: max 46, median (IQR)	0.0 (2)
MASES score: max 13, median (IQR)	0.5 (2)
Dactylitis count: max 20, median (IQR)	0.0 (0)
Tender point count: max 18, median (IQR)	1.0 (4)
BASMI: max 10, mean (S.D)	2.8 (1.1)
BASDAI: max 10, mean (S.D)	3.8 (2.1)
BASFI: max 10, mean (S.D)	2.8 (2.1)
BASG: max 10, mean (S.D)	4.1 (2.3)
Harvey-Bradshaw Index: remission, n (%)	13 (65.0)[d]

Table 2: General and axSpA characteristics of participants who attended the clinical assessment visit of the Clinical Strategy Study (part 2).

Partial Mayo Index: remission, n (%)	56 (90.3)[d]
Investigations	
HLA-B27 positive, n (%)	6 (7.3)
CRP: crude, mg/L, mean (S.D.)	4.3 (7.2)
ESR: crude, mm/h, mean (S.D.)	13.9 (15.7)
Fulfilled radiological criteria for mNYC, n (%)	5 (6.1)
Fulfilled ASAS MRI SIJ positive criteria, n (%)	3 (3.9)[d]
Fulfilled ASAS MRI spine positive criteria, n (%)	1 (1.3)[d]

Table 3: General and axSpA characteristics of participants who attended the clinical assessment visit of the Clinical Strategy Study (part 3).

[a]Note that these characteristics were all rheumatologist verified items during dedicated clinical visit. [b]Rheumatologist's IBP is the investigator's global impression of whether the back pain is of an inflammatory nature via a medical interview. [c]Number of other co-morbidities: Number of past and concurrent medical conditions reported at the visit. [d]Total observations use for the calculation of the summary statistic is not n=82.

axSpA: axial spondyloarthritis; ASAS: Assessment in SpondyloArthritis International Society; CBP: chronic back pain; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HLA-B27: human leucocyte antigen B27; IBP: inflammatory back pain; imp: impression; mNYC: modified New York criteria; MSK: musculoskeletal; n: number/count/frequency; PROMs: patient-reported outcome measures; SIJ: SI joint; SpA: spondyloarthritis.

Patient Characteristics[a]	Eligible patients who attended the clinical assessment visit (n=82)
IBD characteristics	
Type of IBD	-
Crohn's Disease, n (%)	21 (25.6)
Ulcerative Colitis, n (%)	61 (74.4)
Age of IBD symptoms onset: years, mean (S.D.)	31.0 (14.5)
Age of IBD diagnosis: years, mean (S.D.)	35.0 (14.6)
Duration of IBD[b]: months, mean (S.D.)	202.4 (158.3)
Majority of UC disease extent: left-sided, n (%)	27 (44.3)[d]
Majority of CD disease location: ileal, n (%)	11 (52.4)[d]
Majority of CD disease behaviour: inflammatory, n (%)	12 (63.2)[d]
IBD treatment and disease activity	
Previously had IBD treatment, n (%)	80 (97.6)
Currently on IBD treatment, n (%)	70 (85.4)
rectal topical steroids, n (%)	6 (7.3)
oral steroids, n (%)	2 (2.4)
rectal topical 5ASA, n (%)	8 (9.8)
oral 5ASA, n (%)	55 (67.1)
immunosuppression e.g. AZA/MTX, n (%)	23 (28.1)
biologics, n (%)	0 (0.0)

Table 4: IBD characteristics of participants who attended the clinical assessment visit of the Clinical Strategy Study (part 1).

Previously surgery for IBD, n (%)	13 (15.9)
Hospitalisation for IBD, n (%)	38 (46.3)
Patient reported - current IBD disease activity: remission, n (%)	40 (48.8)
Patient reported - gastroenterologist's imp of current IBD disease activity: remission, n (%)	48 (58.5)
Gastroenterologist verified disease activity in the last year: remission[c], n (%)	54 (65.9)

Table 5: IBD characteristics of participants who attended the clinical assessment visit of the Clinical Strategy Study (part 2).

[a]Note that these characteristics were all rheumatologist-verified items during dedicated clinical visit. [b]Duration of IBD is period between formal diagnosis of IBD by gastroenterologist to age at visit. [c]Gastroenterologist-verified disease activity in the last year: Remission is clinical and/or endoscopic remission for >12 months. [d]Total observations use for the calculation of the summary statistic is not n = 82.

CD: Crohn's disease; IBD: inflammatory bowel disease; imp: impression; n: number/ count/frequency; UC: ulcerative colitis.

3.3.2 *Agreement of RVD-axSpA and LoC*

There was fair agreement (k = 0.25; 95% CI: 0.07, 0.51) with a median LoC of 7 (IQR 6–8) of RVD-axSpA based on clinical information before investigative results. After considering investigation results (i.e. CRP, ESR, HLAB27, X-ray, MRI findings) and discussion of discrepant cases, the final agreement was almost perfect (k = 0.92; 95% CI: 0.55, 0.99) with a median LoC of 9 (IQR 8–9).

3.3.3 *Prevalence of undiagnosed and total axSpA*

The prevalence of undiagnosed RVD-axSpA was estimated to be between 1% to 5% in IBD patients. The estimated prevalence of total RVD-axSpA in all patients who were sent a SQ is 2.3%. See Table 6 for different permutations of various prevalence of axSpA/sacroiliitis. The fulfilment of various classification criteria for axSpA were 39% (ESSG), 12% (ASAS) and 5% (mNYC) and are shown in Table 7.

3.3.4 *SNAC group*

Forty-one patients were eligible for clinical assessment. The mean age was 63 years, 44% were male, 76% had ulcerative colitis, 24% Crohn's disease and 68% were in remission. One patient (1/40; 2.5%) had asymptomatic sacroiliitis as shown in Figure 7. A second patient had undiagnosed RVD-axSpA [prevalence was 1/41 or 2.4% (95% CI 0.1, 12.9)] as shown in Table 6.

Case definition	Base IBD population definition	Cases, n	Base, n	Prevalence[a], %
Undiagnosed axSpA[b]	Patients c/o sCBP who had CA	4	82	4.9
Undiagnosed axSpA	Patients w/o sCBP who had CA	1	41	2.4
Undiagnosed axSpA	All patients who had CA	5	123	4.1
Undiagnosed axSpA	All patients who returned a valid SQ[e]	5	173	2.9[f]
Undiagnosed axSpA	All patients who were sent a SQ	5	470	1.1[f]
All axSpA	All patients who were sent a SQ	11	470	2.3[f]
Symptomatic sacroiliitis[d] (sCBP but no axSpA)	Patients c/o sCBP who had CA	5	82	6.1
Asymptomatic sacroiliitis (No sCBP)	Patients w/o sCBP who had CA	1	40[g]	2.5

Table 6: Various prevalence of axSpA/sacroiliitis in IBD patients.

[a]This table explains the prevalence in percentage with reference to Figure 7: Flow chart of N-ASPIRE Clinical Strategy Study.; Prevalence = Case/Base × 100%. [b]axSpA refers to RVD-axSpA. [c]CA refers to the group that had a clinical assessment for axSpA in the study. [d]Sacroiliitis refers to imaging meeting the radiological criteria of mNYC and/or ASAS. [e]Valid SQ refers to those who are eligible for CA. [f]This estimate assumes that all other cases in the base population do not have a clinical diagnosis of axSpA. [g]only 40/41 MRI scan had full protocol acquisition.

axSpA: axial spondyloarthritis; ASAS: Assessment in SpondyloArthritis International Society; CA: clinical assessment; c/o: complaining of; IBD: inflammatory bowel disease; mNYC: modified New York criteria; RVD: rheumatologist-verified diagnosis; sCBP: self-reported chronic back pain >3 months, age onset <45 years old; SQ: screening questionnaire; w/o: without.

axSpA definition	Cases, n	Total, n	Prevalence[a], %
Rheumatologist verified diagnosis of axSpA, n (%)	4	82	4.9
Fulfilled ESSG criteria[b] for SpA, n (%)	32	82	39.0
Fulfilled ASAS criteria[b] for axSpA (clinical or imaging arm), n (%)	9	78[c]	11.5
Fulfilled ASAS imaging arm[b] only, n (%)	7[d]	78	9.0
Fulfilled ASAS clinical arm[b] only, n (%)	2	78	2.6
Fulfilled mNYC criteria for AS[b], n (%)	4	82	4.9

Table 7: Prevalence of axSpA using different criterion.

[a]Prevalence = Case/Total × 100%. [b]The fulfilment of various classification criteria regardless of the clinical diagnosis is shown only as an illustration. Classification criteria should not be used as diagnostic criteria. [c]MRI results were missing in four cases; these did not have a clinical diagnosis of axSpA. [d]Distribution: two cases fulfilled the ASAS definition of a positive MRI; four cases fulfilled mNY radiological criteria; one case fulfilled both criteria.

axSpA: axial spondyloarthritis; ASAS: Assessment in SpondyloArthritis International Society; mNYC: modified New York criteria; n: number/count/frequency; SpA: spondyloarthritis.

3.4 Discussion

A link between axSpA and IBD is well established. Despite an improved understanding of the spectrum of axSpA, there continues to be a significant diagnostic delay in axSpA. Referral strategies have been developed to screen the general population and those presenting with acute anterior uveitis [12,107]. Previous studies have reported the prevalence of axSpA spectrum disease in IBD in different care settings, study designs and a range of axSpA case definitions [50]. Few studies [85–87] have explored the burden of undiagnosed axSpA in the IBD population as their main study outcome.

In our observational cross-sectional study, the prevalence of undiagnosed RVD-axSpA in IBD patients seen routinely in a hospital setting with self-reported CBP (>3 months), onset age <45 years, is estimated at 4/82 (5%). This represents a significant hidden disease burden as it is 4/10 (40%) of the total RVD-axSpA in our sample. This study is important for several reasons. Firstly, this provides the first estimate of undiagnosed RVD axSpA in IBD patients based on modern axSpA concepts which mirrors standard daily clinical practice. Previous studies included in a recent systematic review showed that most cross-sectional prevalence studies either collected their data retrospectively or if collected prospectively, the proportion of undiagnosed patients were not specified [50]. It also highlights the absence of adequate contemporary studies that reflect the current population and practice [85,86].

The diagnoses made by the rheumatology panel had good agreement and a high level of confidence. If the diagnosis was based on classification criteria only (see Table 7), our estimates would have aligned with a previously reported pooled prevalence of sacroiliitis (mostly defined with imaging) of 10% [1]. AxSpA remains a clinical diagnosis based on suspicious symptoms supported by laboratory and imaging investigations; the fulfilment of classification criteria does not necessarily equate to a diagnosis of axSpA. In addition, biological therapy should not be given to patients without a clinical diagnosis of axSpA regardless of imaging or classification results.

The study found a low prevalence of sacroiliitis and undiagnosed RVD-axSpA in the asymptomatic sample. AxSpA typically presents with a history of chronic back pain [133]. However, asymptomatic sacroiliitis has been reported in patients with IBD [137] who have MRI findings resembling axSpA [138]. Results from the SNAC group found only a single case of asymptomatic sacroiliitis. Although this is lower than the prevalence reported by previous studies [137,139–141], it is most likely due to the varying definition of 'asymptomatic' between studies. We used the absence of self-reported CBP for >3 months and onset age <45 years as 'asymptomatic' a priori because the clinical probability of RVD-axSpA is less likely. This is further substantiated as our results showed that in IBD patients without self-reported CBP, there was only a single case of undiagnosed RVDaxSpA.

In the clinical context, it is extremely important to correlate the clinical phenotype with imaging findings depending on the clinicians' pre-test probability of axSpA before arriving at a diagnosis of axSpA. This is even more important in IBD as there is a known background prevalence of asymptomatic sacroiliitis as described above. Our study provides more understanding about symptomatic sacroiliitis vs a diagnosis of axSpA (see Figure 7). Previous studies [113,132,139,140,142] have reported symptomatic sacroiliitis, with prevalence ranging from 3% to 45% (due to broad range of definitions). It must be remembered that imaging evidence of sacroiliitis represents supportive evidence of previous or current inflammatory changes at the sacroiliac joints depending on the modality and timing of imaging, but this is not a confirmation of an autoinflammatory or autoimmune cause, without accompanying clinical context/ evidence. In this study, 5/82 (6.1%) who had self-reported CBP >3 months and onset age <45 years had symptomatic sacroiliitis (meeting the radiological criteria of mNYC and/or ASAS) but did not reach a clinical diagnosis of axSpA as shown in Figure 7 and Table 6. Also, it is interesting to note that the prevalence of symptomatic sacroiliitis is higher than undiagnosed RVD-axSpA (6.1% vs 4.9%, see Table 6). This may suggest that it is important to seek expert opinion from specialist rheumatologists in complex cases, as clinical judgement/ experience and consensus are needed rather than the application of criteria or reliance on imaging alone when reaching a diagnosis of axSpA in IBD patients.

The presence of back pain alone may not be a reliable indicator of RVD-axSpA in the IBD population. In the study, the prevalence of

self-reported CBP (>3 months, onset age <45 years) that might raise the suspicion of axSpA in IBD patients is 91/173 (53%). This is higher than the estimate of CBP in the general population, with an upper limit of 20% in a recent systematic review [143]. When we apply the Calin, Berlin, ASAS inflammatory back pain criteria, this translates to 31/91 (34%), 29/91 (32%) and 24/91 (26%), respectively. However, in patients that were assessed clinically, 82/91 (90%), a majority 78/82 (95%) did not result in a final inflammatory disease diagnosis. The other diagnoses included spondylosis 56/78 (72%), fibromyalgia 1/78 (1%), nonspecific lower back pain 6/78 (8%), no specific differential diagnosis 2/78 (3%), and other overlapping noninflammatory diagnosis 13/78 (17%).

This study has several limitations. Firstly, this was a cross sectional design. Secondly, some degree of selection bias may have been introduced as the sample was from a single centre and excluded patients treated with biologic therapy which could have modified the symptoms, laboratory biomarkers, MRI findings and interpretation, as well as the impact on the ability to diagnose AxSpA with confidence. Also, excluding patients treated with biologics for IBD may have excluded patients with concomitant axSpA limiting generalisability. In addition, due to the cut-off age of onset of chronic back pain in the eligibility criteria, axSpA patients with late onset IBD (IBD onset >45 years) may have been excluded. Finally, we did not clinically re-evaluate those with a pre-existing diagnosis of axSpA, so it is theoretically possible that some

of these could have been misdiagnosed. Taken together, the prevalence of undiagnosed RVD-axSpA may be underestimated.

Furthermore, due to ethical and financial constraints, we were unable to sample the whole population (especially those without self-reported back pain). However, a sample in the form of the SNAC group was performed with its limitations. The study assessment protocol for the SNAC group was the same as those in the screen positive group except for pelvic radiography due to ethical concern over radiation exposure. Nonetheless, we had axSpA-protocoled MRI imaging for all 41 patients who attended the clinical assessment (except one who did not complete a full protocol acquisition). In this patient, available imaging was sufficient for clinical reporting but not ASAS criteria reading. It is unlikely that we failed to detect any case of sacroiliitis on imaging due to this process.

Also, as the SNAC group consisted of patients without self-reported CBP (>3 months and onset age <45 years) it is likely that the mean age will be older than the screen positive group, thus the selection for the SNAC group were matched to the nearest age and sex to ensure that the groups were matched. Due to the small sample to select from (n = 51), this was not entirely possible. Further sub-analysis showed that there was no difference in the percentage of males between the screen positive and SNAC groups (37% vs 44%, P = 0.62), but the mean age of the SNAC group was older despite best attempts at matching (63 vs 52 years, P < 0.0001). A difference in age may theoretically result in more age-related MRI changes at the sacroiliac joints, which may affect the outcome of

reported asymptomatic sacroiliitis. Nevertheless, the results are reassuring as there was only one asymptomatic sacroiliitis and one undiagnosed RVD-axSpA.

We believe that we now have a clearer understanding of the magnitude of the hidden burden of axSpA in IBD. Further work will need to focus on reproducing this estimate in other national and international cohorts and developing screening tools to allow early identification and referral of IBD patients for rheumatology assessment. At present, one should still follow the guidance of the ASAS-endorsed recommendation for the early referral of patients with suspected axSpA [101]. This should work in parallel with campaigns and educational strategies to raise awareness of this disease association.

In conclusion, the results of this study have practical implications, as they show that there is undiagnosed RVD-axSpA among patients attending secondary care IBD clinics. To our knowledge, this is the first attempt to estimate the prevalence of undiagnosed RVD-axSpA in IBD patients, based on our current understanding of axSpA in daily clinical practice. The importance of a clinical diagnosis in axSpA is made clearer by understanding the background of asymptomatic and symptomatic sacroiliitis in IBD patients. Appropriate identification of suspected axSpA patients in IBD clinics offers an opportunity to shorten the delay to diagnosis in axSpA.

Chapter 4. N-ASPIRE Imaging Strategy Study

4.1 Introduction

This chapter describes the imaging referral strategy through the design of the N-ASPIRE Imaging Strategy Study. The study also estimated the proportion of IBD patients, with imaging-compatible changes (when undertaken for non-musculoskeletal indications), who have undiagnosed axSpA diagnosis verified by a rheumatologist. In addition, the study assessed the utility of a known screening tool to facilitate the identification of axSpA diagnosis in this specific IBD population.

4.2 Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee East of England – Essex Research Ethics Committee (252117 19/EE/0125). All participants gave written informed consent before study inclusion.

4.2.1 Design

The study was a cross-sectional study. Patients with IBD who were retrospectively identified to have Computed Tomography-defined Sacroiliitis (CTSI) underwent a prospective clinical assessment, to determine what proportion have Rheumatologist-Verified Diagnosis of axial spondyloarthritis (RVD-axSpA). This is shown diagrammatically in Figure 8, Figure 9 and Figure 10; it will be described further in the paragraphs below.

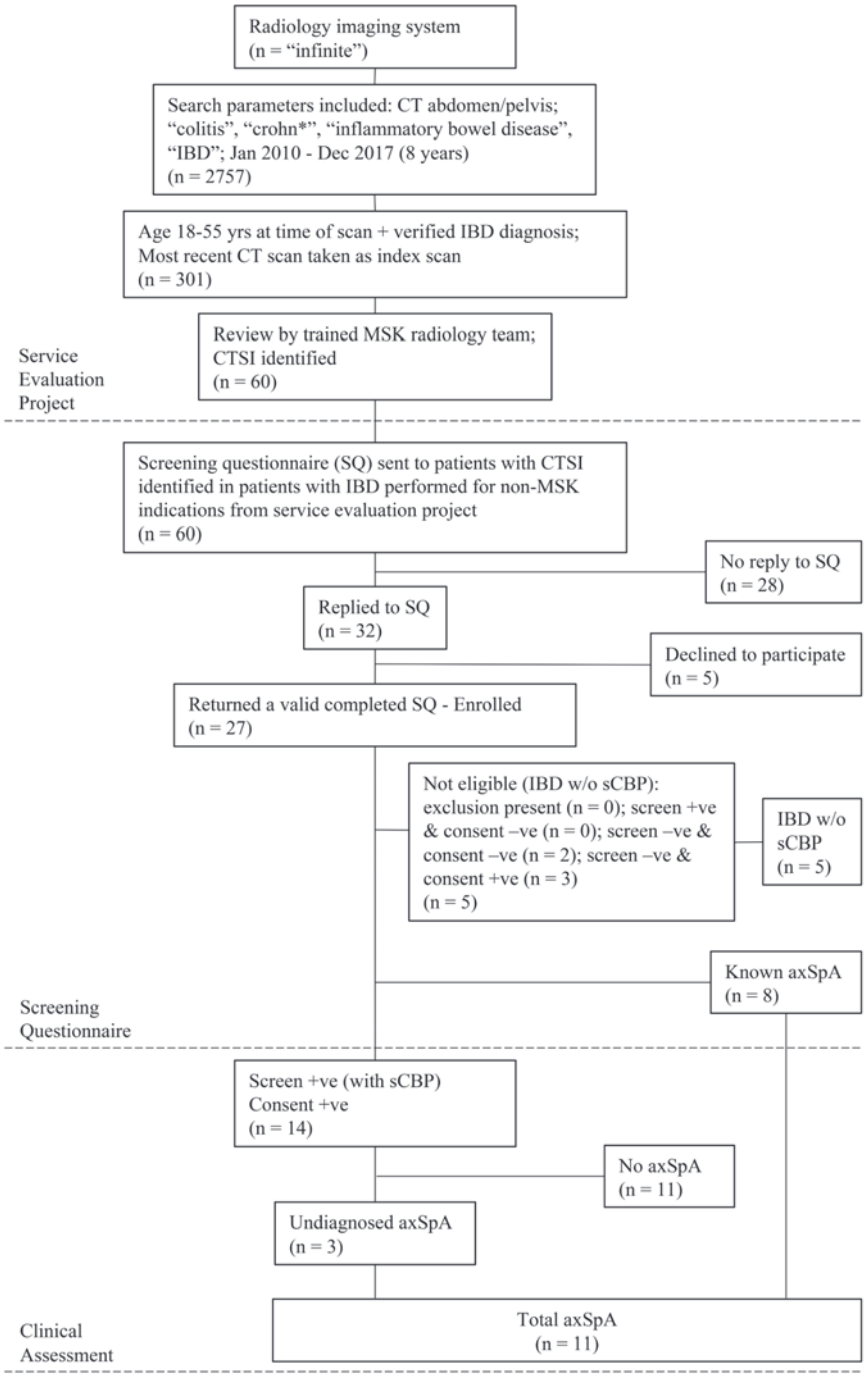

Figure 8: Flow chart of the N-ASPIRE Imaging Strategy Study.

Figure by author. –ve: negative; +ve: positive; axSpA: axial spondyloarthritis; CT: computed tomography; CTSI: computed tomography–defined sacroiliitis; IBD: inflammatory bowel disease; MSK: musculoskeletal; sCBP: self-reported chronic back pain with duration of > 3 months and age of onset of < 45 years; w/o: without.

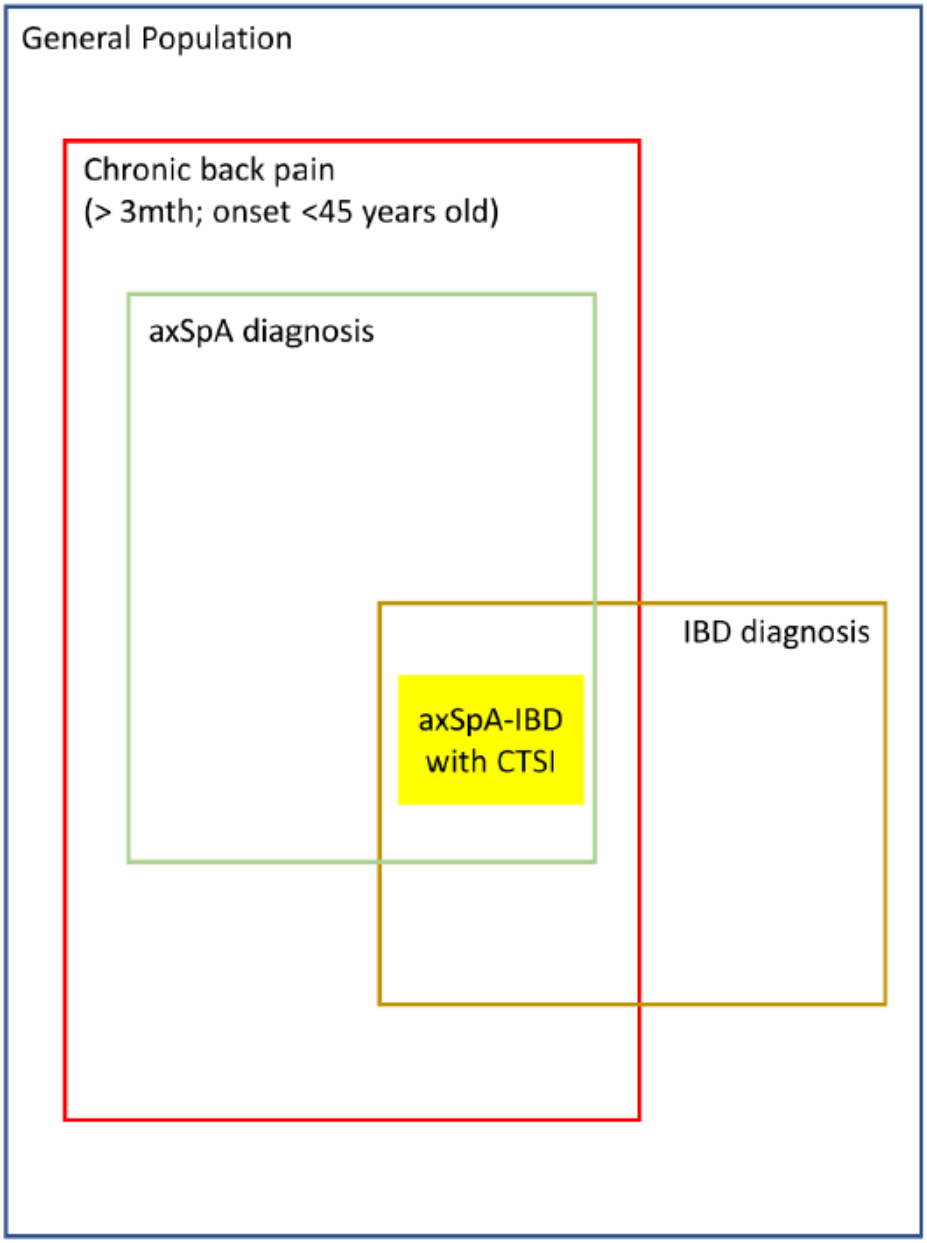

Figure 9: Box Venn Diagram of axSpA and IBD

Figure by author. axSpA: axial spondyloarthritis; CTSI: computed tomography defined sacroiliitis; IBD: Inflammatory Bowel Disease; mth: month

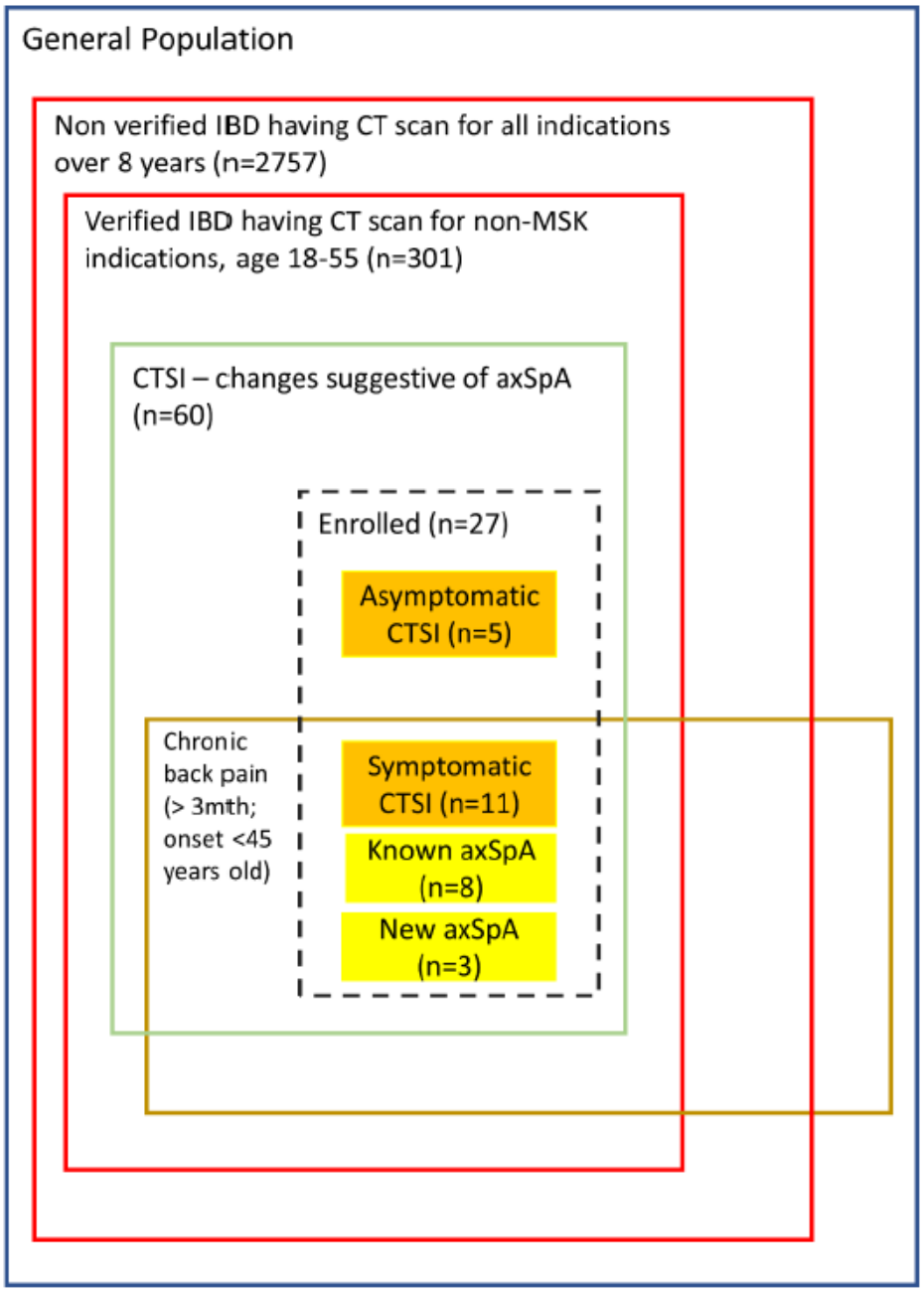

Figure 10: Box Venn Diagram of CTSI and symptoms in the context of axSpA and IBD.

Figure by author. axSpA: axial spondyloarthritis; CT: Computed Tomography; CTSI: CT-defined sacroiliitis; IBD: Inflammatory Bowel Disease; mth: month; msk: musculoskeletal

4.2.2 *Identification of the Study Population*

The study population was selected from a service evaluation project performed at Norfolk and Norwich Hospital. Abdominopelvic CT scans of patients with verified IBD (Crohn's disease or Ulcerative Colitis, diagnosed by gastroenterologist via gastroenterology clinical letter, and supportive histology or radiology results using electronic medical, laboratory, and radiology records) were retrospectively identified from the radiology imaging system between January 2010 to December 2017. The study population was limited to 18 to 55 years of age, inclusive, at the time of their CT, with the most recent CT named the index scan. The age range of 18 to 55 years old was chosen as the interval which will be of highest diagnostic yield, and would capture almost all cases of disease with symptom onset at or before 45 years old [144] given the diagnostic delay window of approximately 8-10 years [36,93]. The scans were reviewed by radiologists trained to identify radiological features of CTSI using the criteria developed by Chan et al [117], after internal reliability testing and clarification.

4.2.3 *Definition of criteria that define Computed Tomography defined sacroiliitis (CTSI)*

Chan et al [117] developed a pragmatic screening tool for the identification of sacroiliitis on abdominopelvic CTs. They have suggested that the criteria can be implemented in the reading of CT scans of high-risk patients such as those with IBD.

They defined the features of CT sacroiliitis in the following manner. *Surfaces*: 4 surfaces – R iliac, L iliac, R sacral, L sacral; Anatomy of

the sacroiliac joint – Erosions and sclerosis are recorded only if present along the cartilaginous component. Lesions along the fibrous component are not counted. *Erosions*: Erosions had to have a clear break in subchondral bone with a minimum depth of 2mm; Large erosions are erosions seen on more than 1 slice; Counting the maximum number of erosions from the worst slice from each articular surface; Osseous abnormalities at the transition point from cartilaginous to fibrous compartment were not scored as erosions; Subchondral cysts are radiolucent lesions without a clear break in the subchondral bone and lesions where the break was ambiguous are not included. *Sclerosis*: Sclerosis is only read from the coronal view and defined as an increase in bone density of at least 1cm in length parallel to the joint line when compared to the midline of the sacrum and scored as present/ absent; The depth of sclerosis is evaluated on the slice with the longest visible cartilage length and noted as extending either >3mm or >5mm perpendicular to the joint line. Sclerotic segments are only measured in areas of homogeneous density as patchy density is poorly reproducible. The initial 5mm at the cranial and caudal ends of the joint where there can be a normal increase in density are not scored. *Ankylosis*: Ankylosis was defined as contiguous bone marrow between the ilium and sacrum >1 cm in length within the cartilage compartment of the joint. If a joint was scored as having ankylosis, neither erosion number nor presence of sclerosis was noted because these changes would be obscured by the ankylosis.

4.2.4 *Clarification and reliability of the radiological features of sacroiliitis on CT*

Three radiology registrars were trained by an experienced musculoskeletal (MSK) radiologist with >20 years of experience. All radiologists were blinded to the clinical information and the original radiology report. Thirty cases were randomly chosen for training and scored by the 3 readers over an interval of 2 weeks.

Reliability statistics were calculated using the weighted kappa coefficient of agreement. The initial interrater reliability was moderate to substantial (kw = 0.59 - 0.70, 95% CI 0.36 - 0.82 to 0.40 - 1.00). Discordant scores were settled at a consensus meeting between the readers and the experienced MSK radiologist. From this, the following points were added to the erosion definition: (a) Erosions are breaks seen on either the axial or coronal view, (b) The erosion depth is to be rounded down to 1mm if measurement is </=1.49mm and rounded up to 2mm if measurement is >/=1.5mm, (c) Erosions are included if they involve the joint proper. Bony defects/irregularity seen at the inferior margin of the bony pelvis are excluded.

Following an 8-week interval from the consensus meeting, the same 30 patients were re-scored to assess intra and inter-rater reliability. This resulted in substantial agreement (kw = 0.66 - 0.77, 95% CI 0.46 - 0.87 to 0.63 - 0.90) with moderate to almost perfect intra-rater reliability (kw = 0.47 - 0.85, 95% CI 0.20 - 0.72 to 0.74 - 0.97). There was an improvement in interrater reliability following training and clarification of the erosion definition.

After a further 8-week interval from the re-scoring exercise, the cases were randomly divided between readers to identify radiological features of CTSI. As our sampled population was enriched (with IBD diagnosis and age range within the highest diagnostic yield for axSpA), we selected the criteria which were shown to have the highest sensitivity (94%) by Chan et al to identify cases of sacroiliitis that were suspected to co-occur with axSpA, so that all possible cases were included.

4.2.5 Study Population

Screening questionnaires (SQ) were sent to all patients with (a) CT performed for non-MSK indications; (b) Age between 18 and 55 years of age inclusive at the time of CT; (c) IBD diagnosis (by gastroenterologist with supporting histology or radiology results); (d) Presence of CTSI, defined as the presence of sacroiliac joint ankylosis, total erosion score (TES) of ≥3, > 0.5 cm iliac sclerosis and/or > 0.3 cm sacral sclerosis. Those who replied with a valid completed SQ and gave informed consent were enrolled. Those with chronic back pain > 3 months, age onset < 45 years were invited for rheumatology assessment. Those with pre-existing confirmed axSpA, verified from their medical records were contacted via telephone to collect clinical characteristics but were not reassessed.

4.2.6 Clinical Assessment

Clinical assessment included a full medical interview; physical examination by a rheumatologist, including joint and tender point count, the MASES, dactylitis count, BASMI; patient-reported outcomes, including the BASDAI, BASFI, BASG, the Harvey-Bradshaw-Index, Partial-Mayo-Index; laboratory tests including CRP, ESR, HLA-B27; and dedicated MRI sequences for axSpA detection (similar to clinical study, see 3.2.4 Clinical assessment)

4.2.7 Diagnosis Verification

Each subject was discussed in two virtual meetings: an initial discussion solely based on clinical history and examination findings, and a second following the availability of laboratory and imaging results. The panel comprising three expert rheumatologists with a specialist interest in axSpA were blinded to the CT findings (sclerosis, erosions and/or ankylosis). Each made either a positive or negative diagnosis of axSpA. They also indicated their level of confidence on a 10-point Likert scale. RVD-axSpA was confirmed when at least two rheumatologists agreed. A level of confidence (LoC) was reflected by an average of the three Likert scales. A similar process was undertaken when the results of MRI and laboratory results were available. Any discrepancy (i.e. change of diagnostic category or reduced LoC) between the pre- and post- investigation diagnosis was discussed in a further summary meeting, and a final diagnosis made by a majority consensus vote after a subsequent review of all clinical, laboratory and MRI information.

4.2.8 *Definition of CT Screening Tool and retrospective analysis*

The presence of sacroiliac joint ankylosis or total erosion score (TES) ≥3 was defined by Chan et al [117] as sufficient to identify patients as having sacroiliitis with suspected axSpA that may warrant a rheumatologist referral. Chan et al highlighted that sclerosis alone has a lower specificity and lower positive likelihood ratio than the other features (erosions and ankylosis), thus sclerosis was excluded from their final definition.

4.2.9 *Power calculation and statistical analysis*

Estimates of the proportion of RVD-axSpA in those IBD patients with CTSI were unknown. Instead, sample size was estimated from symptomatic CTSI (arrange of 3% to 45%) [132,139,140]. It was estimated that 21 patients were needed to detect a minimum symptomatic CTSI proportion of 30% (derived from clinical experience at our institution) at a nominal threshold significance of P = 0.05. Based on the assumptions that 50% of these patients would respond to the SQ and that 80% of the respondents would take up an invitation for clinical review, the study aimed to screen an initial sample of 54 patients with IBD.

Descriptive statistics were used to summarize the patient characteristics, stratified by symptoms and diagnosis. For calculation of proportions, the frequency of cases (i.e. RVD-axSpA) to the base population (i.e. IBD patients with CTSI) was used with a calculated confidence interval. Inter-clinician diagnostic agreements were calculated using kappa statistic with estimated

confidence intervals. Descriptive statistics were used to present the average LoC. The efficacy of the CT Screening Tool in predicting a final diagnosis of axSpA was measured in terms of sensitivity, specificity, positive and negative predictive values. Data analysis was performed using STATA Version 15 (StataCorp, TX, USA) and Microsoft Excel 2016 (Microsoft, WA, USA).

4.3 Results

4.3.1 Service evaluation results

Three hundred and one unique scans of patients with verified IBD (mean age 36; female 50.8%) were reviewed by the radiology team (see Figure 8 and Figure 10). A total of 60/301 (19.9%) of these patients were identified as having CTSI. Among 248 CD and 53 UC patients, the proportion of CTSI were 51/248 CD (20.6%) and 9/53 UC (17.0%) respectively. The accompanying radiology report of these 60 positive scans for CTSI were reviewed. Only 15 (25%) of these cases were reported as showing sacroiliitis with no recommendation made for onward rheumatological evaluation. Of the remaining 45 CTSI: 26 were unrecognised despite the report documenting a bone review, 17 did not mention a bone review, and 2 were unrecognised despite the SI joints having apparently been reviewed. In summary, 1 in 5 selected patients with IBD had sacroiliitis suggestive of axSpA but this was not reported in 3 out of 4 scans.

4.3.2 Study patient characteristics and axSpA diagnosis

In total, 60 patients were sent a SQ. In total, 32 (53%) patients responded to the invitation to participate and 27 (84%) were enrolled (see Figure 8 and Figure 10). The detailed clinical characteristics of these patients are shown in Table 8-10 . Out of 27 patients, 14 (51.9%) were invited for rheumatology assessment, as 8 (29.6%) had a prior diagnosis of axSpA, and 5 (18.5%) did not report CBP. Out of these 14 patients, 3 (21.4%, 95% CI 4.7-50.8) had undiagnosed RVD-axSpA. The other diagnoses included spondylosis (5/14, 36%), fibromyalgia (5/14, 35.7%), and nonspecific lower back pain (1/14, 7.1%). In total, 11 of the 27 (40.7%, 95% CI 22.4-61.2) enrolled patients had RVD-axSpA. See Table 11 for different permutations of various proportions of axSpA/sacroiliitis.

Characteristics[b, g]	Asymptomatic CTSI (n=5)	Symptomatic CTSI[c] (n=11)	Known axSpA[d] (n=8)	Un-diagnosed axSpA[c] (n=3)	ALL CTSI (n=27)
Demographics					
Gender: female	1 (20.0)	7 (63.6)	1 (12.5)	3 (100.0)	12 (44.4)
Age at CT scan[a]: years	36.6 (6.7)	33.6 (7.6)	43.9 (9.0)	39.0 (6.1)	41.2 (7.0)
Age at presentation to rheumatology[e]: years	43.2 (6.1)	39.7 (6.8)	40.8 (14.2)	44.7 (6.1)	41.2 (9.2)
CBP Characteristics					
Presence of CBP[f]: yes	0 (0.0)	11 (100.0)	8 (100.0)	3 (100.0)	22 (81.5)
Age of onset of CBP: years	-	21.9 (5.7)	27.3 (9.8)[b]	31.0 (10.5)	24.9 (8.2)[b]
IBP Calin	0 (0.0)	5 (45.5)	4 (50.0)	2 (66.6)	11 (40.7)
IBP Berlin	0 (0.0)	4 (36.4)	3 (37.5)	3 (100.0)	10 (37.0)
IBP ASAS	0 (0.0)	5 (45.5)	3 (37.5)	1 (33.3)	9 (33.3)
Other relevant axSpA history					
Positive personal history of axSpA conditions (Not IBD)	0 (0.0)	3 (27.3)	5 (62.5)	2 (66.7)	10 (37.0)
Positive personal history of inflammatory peripheral MSK pain: yes[h]	0/1 (0.0)	0 (0.0)	1/5 (20.0)	2 (66.7)	3/20 (15.0)

Table 8: Clinical characteristics of IBD patients with CTSI in the Imaging Strategy Study (part 1).

Acute anterior uveitis[h]	0 (0.0)	1 (9.1)	1/7 (14.3)	0 (0.0)	2/26 (7.7)
Skin psoriasis	0 (0.0)	2 (18.2)	3 (37.5)	1 (33.3)	6 (22.2)
Positive family history of axSpA conditions	0 (0.0)	5 (45.5)	5 (62.5)	1 (33.3)	11 (40.7)
IBD characteristics					
Crohn's Disease	3 (60.0)	10 (90.9)	7 (87.5)	2 (66.7)	22 (81.5)
Ulcerative Colitis	2 (40.0)	1 (9.1)	1 (12.5)	1 (33.3)	5 (18.5)
Age of IBD symptoms onset: years	26.6 (6.5)	17.6 (6.9)	30.8 (13.5)	31.0 (8.2)	24.7 (10.8)
Age of IBD diagnosis: years	27.6 (6.2)	23.3 (7.3)	31.6 (13.1)	34.3 (4.9)	27.8 (9.6)
IBD Dx Delay – duration between IBD symptom onset to diagnosis: years	1.0 (2.0)	3.0 (8.0)	0.0 (1.5)	2.0 (8.0)	2.0 (8.0)
Duration of IBD – duration between IBD diagnosis to rheumatology review: years	15.6 (6.5)	16.4 (7.2)	9.1 (12.2)	10.3 (3.5)	13.4 (8.9)
IBD treatment and disease activity					
Ever use biologics for any indication before presentation	2 (40.0)	4 (36.4)	4 (50.0)	1 (33.3)	11 (40.7)
Patient reported current IBD disease activity: remission[h]	3/4 (75.0)	5 (45.5)	-	1 (33.3)	9/18 (50.0)

Table 9: Clinical characteristics of IBD patients with CTSI in the Imaging Strategy Study (part 2).

Last gastroenterologist record of IBD disease activity: remission[h]	3 (60.0)	9 (81.8)	5/5 (100.0)	3 (100.0)	20/24 (83.3)
Examination and PROMs					
BMI: kg/m2[j]	-	29.0 (8.1)	-	25.8 (6.0)	28.3 (7.6)[b]
BASMI: max 10[j]	-	2.1 (0.6)	-	2.4 (0.7)	2.4 (1.0)[b]
BASDAI: max 10[h]	-	4.0 (2.1)	5.8 (1.2)[b]	4.9 (2.9)	4.7 (2.1)[b]
BASFI: max 10[h]	-	3.2 (2.7)	3.5 (1.5)[b]	2.2 (2.2)	3.1 (2.4)[b]
BASG: max 10[j]	-	4.4 (2.8)	-	4.1 (2.0)	4.4 (2.6)[b]
Harvey-Bradshaw Index: remission[i,j]	-	5/10 (50.0)	-	2/2 (100.0)	7/12 (58.3)[b]
Partial Mayo Index: remission[i,j]	-	1/1 (100.0)	-	1/1 (100.0)	2/2 (100.0)
Investigations and Classifications					
HLA-B27 positive[h]	-	1/10 (9.1)	3/7 (42.9)	1 (33.3)	5/21 (23.8)
CRP: crude, mg/L[j]	-	3.0 (3.0)	-	2.0 (11.0)	2.5 (2.0)
ESR: crude, mm/h[j]	-	7.0 (9.0)	-	7.0 (15.0)	7.0 (9.0)
Fulfilled ASAS MRI SIJ positive criteria[h]	-	0 (0.0)	3/6 (50.0)	1 (33.3)	4/20 (20.0)

Table 10: Clinical characteristics of IBD patients with CTSI in the Imaging Strategy Study (part 3).

[a]CT was done for non-MSK indications. [b]Initial data was collected prospectively via a questionnaire for all groups. [c]Symptomatic CTSI and Undiagnosed axSpA group underwent further clinical assessment prospectively. [d]Data from Known axSpA is collected from further case notes and telephone review. [e]Age at presentation to rheumatology is taken as the date of first rheumatology assessment for all groups except Asymptomatic CTSI which was taken to be date of enrolment into study. [f]Chronic back pain is defined as intermittent/continuous back pain/stiffness lasting a total duration of more than 3 months. [g]Except where indicated otherwise, values are the n (%); mean

(S.D.); median (IQR); [h]Different base total due to missing data, which is excluded from relative frequency calculation; [i]Subgroup analysis; [j]Prospective clinical assessment data only; - No data.

AS: Ankylosing spondylitis; ASAS: Assessment in SpondyloArthritis international Society; axSpA: axial spondyloarthritis; AZA: azathioprine; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASG: Bath Ankylosing Spondylitis Global Score; BASMI: Bath AS metrology index; BMI: body mass index; CBP: chronic back pain; CD: Crohn's Disease; CRP: C-reactive protein; CT: computed tomography; CTSI: CT-defined sacroiliitis; Dx: diagnosis; ESR: erythrocyte sedimentation rate; ESSG: The European Spondyloarthropathy Study; HLA-B27: human leukocyte antigen B27; IBD: inflammatory bowel disease; IBP: inflammation back pain; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MRI: magnetic resonance imaging; MSK: musculoskeletal; MTX: methotrexate; n: number/count/frequency; NSAIDs: Non-steroidal anti-inflammatory drugs; PROMs: patient reported outcome measures; SIJ: sacroiliac joint; SpA: Spondyloarthropathy; UC: Ulcerative Colitis

Case Definition	Base Population Definition	Cases, n	Base Population, n	Proportion[a], %
Undiagnosed axSpA[b]	All patients who had CA[c]	3	14	21.4
Undiagnosed axSpA	All patients who returned a valid SQ[d]	3	27	11.1
All axSpA	All patients who returned a valid SQ	11	27	40.7
All axSpA	Patients c/o sCBP who had CA	11	22	50.5
Asymptomatic CTSI (No sCBP)	All patients who returned a valid SQ	5	27	18.5
Symptomatic CTSI (sCBP)	All patients who returned a valid SQ	22	27	81.5
Symptomatic CTSI (sCBP but no axSpA)	All patients who returned a valid SQ	11	27	40.7
All axSpA	All patients who were sent a SQ	11	60	18.3[e]
Undiagnosed axSpA	All patients who were sent a SQ	3	60	5.0[e]

Table 11: Proportions of axSpA/sacroiliitis in patients with IBD.

[a]Proportions are in reference to the Figure 8; proportion = case / base × 100%. [b]AxSpA refers to RVD-axSpA. [c]CA refers to the group that had a clinical assessment for axSpA either in the study or previously by a rheumatologist. [d]Valid SQ refers to the group that returned a valid completed SQ. [e]This estimate assumes that all other cases in the base population do not have a clinical diagnosis of axSpA.

AxSpA: axial spondyloarthritis; CA: clinical assessment; c/o: complaining of; CTSI: computed tomography–defined sacroiliitis; IBD: inflammatory bowel disease; RVD: rheumatologist-verified diagnosis; sCBP: self-reported chronic back pain > 3 months, age of onset < 45 years old; SQ: screening questionnaire.

4.3.3 Agreement of RVD-axSpA and LoC

There was moderate agreement (k = 0.42, 95% CI 0.04 - 0.80) with a median LoC of 6 (IQR 2 - 8) of RVD-axSpA based on only clinical information before investigative results. Once presented with investigation results (i.e. CRP, ESR, HLA-B27, MRI findings), the agreement changed to fair (k = 0.30, 95% CI 0.00 - 0.65) with a median LoC of 7 (IQR 3 - 9). The agreement was substantial (k = 0.74, 95% CI 0.10 - 0.98) with a median LoC of 7 (IQR 5 - 8) for discrepant cases after further discussion. For all cases, the final agreement was almost perfect (k = 0.85, 95% CI 0.35 - 0.97) with a median LoC of 8 (IQR 5 - 9).

4.3.4 Performance of the CT Screening Tool

The utility of the CT Screening Tool was explored in different groups for its performance, retrospectively. The CT Screening Tool was applied to patients who joined the study regardless of having self-reported CBP (analysis 1: patients asymptomatic and symptomatic with CTSI) vs patients with self-reported CBP, CBP duration of greater than 3 months, and age of onset < 45 years based on the SQ (analysis 2: patients symptomatic with CTSI). These results are shown in Table 12 and Table 13. The sensitivity or the ability of the tool to detect patients with RVD-axSpA, was similar for both groups at 90.9%. The specificity values for the groups, or the ability of the tool to correctly reject those without axSpA was 56.3% and 63.6% respectively.

Clinical Diagnosis	Analysis 1[a], n			Analysis 2[b], n		
	Positive	Negative	Total	Positive	Negative	Total
axSpA	10	1	11	10	1	11
No axSpA	7	9	16	4	7	11
Total	17	10	27	14	8	22

Table 12: Analysis of CT screening Tool: Participants in each analysis group.

a Analysis 1 involved applying the screening tool to the group with or without a history of chronic back pain who have an age of onset of < 45 yrs (n = 27). b Analysis 2 involved applying the screening tool to the group with a history of self-reported chronic back pain who have an age of onset of < 45 yrs (n = 22).

AxSpA: axial spondyloarthritis; CT: Computed Tomography.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	DOR
Analysis 1[a]	90.9	56.3	58.8	90.0	2.1	0.2	12.9
Analysis 2[b]	90.9	63.6	71.4	87.5	2.5	0.1	17.5

Table 13: Analysis of CT screening Tool: Performance of the screening tool.

a Analysis 1 involved applying the screening tool to the group with or without a history of chronic back pain who have an age of onset of < 45 yrs (n = 27). b Analysis 2 involved applying the screening tool to the group with a history of self-reported chronic back pain who have an age of onset of < 45 yrs (n = 22).

CT: Computed Tomography; DOR: diagnostic odds ratio; LR–: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

4.4 Discussion

AxSpA is a clinical diagnosis based on suspicious symptoms supported by investigations including imaging [18]. Imaging positive sacroiliitis without symptoms does not automatically imply a diagnosis of axSpA without physician verification. Sacroiliac joint abnormalities can occur for other reasons, including mechanical or degenerative causes, which can manifest as subchondral sclerosis, vacuum phenomenon, and osteophytosis. [35,36]. In addition, targeted therapy should not be given to patients without a clinical diagnosis of axSpA regardless of imaging results. This highlights the importance of understanding what proportion of IBD patients with CTSI have RVD-axSpA. Referral strategies have been published for AAU [107], and questionnaires have been developed to identify spondyloarthritis, using classification criteria, among patients with IBD [109–112]. However, there are no published data on the use of CT as a referral strategy with subsequent confirmation of a rheumatologist-verified diagnosis of axSpA.

We identified that 60 out of 301 (19.9%) of patients with IBD undergoing CT for non-MSK indications had CTSI, and at least 11 out of 60 (18.3%) had RVD-axSpA. In total, 5% (3/60) were previously undiagnosed, despite a mean interval since the index CT scan of 5.7 years and mean duration of back pain of 13.7 years. The validated CT screening tool to identify CTSI was shown to have a sensitivity of 90.9% and specificity of 63.6% for a clinical diagnosis of axSpA. Taken together, this suggests that among an IBD cohort, aged 18 to 55 years, with a CBP duration > 3 months and an age of

onset < 45 years, the tool would be effective in identifying patients with IBD at the highest risk of having RVD-axSpA.

Previous clinical-based studies have shown that 3% to 45% of patients with IBD have symptomatic sacroiliitis seen on plain radiograph and/or CT using a broad range of case definitions for sacroiliitis [132,139,140]. These authors also showed that the proportion of asymptomatic sacroiliitis (i.e. patients with IBD with sacroiliitis but no back pain) ranged from 13.6% to 32% [139–141]. On the other hand, radiology-based studies found that the proportion of incidental/coincidental sacroiliitis on CT in patients with IBD, using various case definitions in IBD patients is between 2.2% and 25% [113–116]. In this study, 22 out of 27 (81.5%) patients with IBD had symptomatic CTSI: 11 out of 27 (40.7%) had RVD-axSpA (3/11 were undiagnosed and 8/11 had known diagnosis) and 11 out of 27 (40.7%) had symptoms but no RVD-axSpA. We also found that 5 out of 27 (18.5%) patients with IBD had asymptomatic CTSI (Figure 10 and Table 11)

This study is important for several reasons. Firstly, the design of the study is novel. It involves a cross-sectional postal survey of patients, supplemented by a structured clinical assessment of a subset of participants to establish the proportion with RVD-axSpA. This is designed to mirror the real-world clinical pathway, whereby if an IBD patient is found to have suspicious sacroiliac changes on imaging, the responsible clinician (the SQ is the surrogate here) will review the patient before onward referral for rheumatology assessment. It is for this reason that the clinical assessment was only performed in those with self-reported CBP > 3 months, onset age <

45 years (which gives a moderate diagnostic probability of axSpA in daily clinical practice).

Secondly, the diagnosis is made by an experienced panel of rheumatologists with a special interest in axSpA, with good agreement and high level of confidence. Given that there is no gold-standard diagnostic biomarker (laboratory, genetic or imaging), the current gold standard is expert opinion. When approaching patients with multisystem complex disease, it can be difficult to make a diagnosis [145]. There is a need to distinguish if the aetiology of sacroiliitis, and back pain, is a result of one or more underlying pathologies. They could include mechanical/degenerative disease; and/or psychological pain overlay of a chronic disease; undiagnosed active inflammatory axial disease; or a combination of both. In this cohort, where the mean disease duration was > 10 years, only 4 out of 9 (44.4%) patients with RVD-axSpA and CTSI had active sacroiliac joint inflammatory lesions on MRI. On the other hand, among patients with a mean disease duration of 17 years with symptomatic CTSI but no diagnosis of RVD-axSpA, none (0/11, 0%) had active sacroiliac joint inflammatory lesions. This could reflect the natural history of inflammatory lesions and highlights the challenges around reliance on structural/inflammatory imaging lesions in making a clinical diagnosis of axSpA in this population. Even in a recent consensus meeting, where the International Organization for the Study of Inflammatory Bowel Disease is developing consensus recommendations for the diagnosis and monitoring of extra-intestinal manifestations for inclusion in IBD clinical trials, this

crucial point may have been overlooked, as 83% of the attendees agreed that the presence of inflammatory back pain with consistent imaging (in this definition MRI) findings would be sufficient for the diagnosis of axSpA without a rheumatologist expertise [112,146].

Thirdly, our study was able to explore the usefulness of a validated imaging tool that may prompt earlier referral to rheumatology, potentially expediting a diagnosis of axSpA. This study shows that by utilising an objective tool and a self-reported screening questionnaire, it is feasible to filter the large numbers of patients with IBD having CT scans down to those with a high pre-test probability of axSpA and arrive at a manageable proportion of patients for clinical assessment. This will ensure that rheumatology services are not overwhelmed and yet are able to identify some undiagnosed axSpA.

This study has several limitations. The study had a cross-sectional design, the sample size was small, and this was a single-centre study. We focused our sample on the population with the highest probability of axSpA; therefore, it is possible that we missed other cases because of selection bias. Also, 33 out of 60 (55%) patients with CTSI did not complete the SQ or declined to participate (Figure 8), thus, their data were not captured. This means that the results may not be generalisable and the prevalence of undiagnosed RVD-axSpA may have been underestimated. Our design did not allow for evaluation of those without CBP, some of whom may have had axSpA; however, it is likely that such patients would have a lower symptom burden and not require targeted therapy. Finally, we did not clinically re-evaluate those with a pre-existing diagnosis of

axSpA, so it is theoretically possible that some of these patients could have been misdiagnosed.

In conclusion, the results of this study may have practical implications, as they show that there is still undiagnosed axSpA among patients with established IBD attending a secondary care institution. It also explores the possibility of using a pragmatic CT screening tool to improve disease awareness among radiologists, aid in axSpA identification, and reduce the delay to diagnosis in this population. The practicalities of implementing this strategy on a wider scale in routine practice will need further research.

Chapter 5. Conclusion

5.1 Summary

AxSpA is closely associated with IBD, but evidence for the contemporary prevalence of undiagnosed axSpA verified by a rheumatologist in IBD patients is sparse. There are referral strategies in primary care and other extra-musculoskeletal manifestations of axSpA, but diagnostic delay still exists. Before we can proceed to develop axSpA referral strategies specific for IBD patients there is a need to quantify the 'hidden burden' or undiagnosed prevalence of axSpA in IBD patients in current daily clinic practice. The principal aims of the project were to estimate the frequency of undiagnosed RVD-axSpA in IBD patients in the secondary care setting and to demonstrate strategies for their identification in contemporary medical practice.

The N-ASPIRE clinical strategy study found that the prevalence of undiagnosed RVD-axSpA in IBD patients seen routinely in a hospital setting with self-reported CBP, is at least 5%. This represents a significant hidden disease burden as it is 40% of the total RVD-axSpA in our sample. The N-ASPIRE imaging strategy study showed that at least 5% of IBD patient undergoing CT for non-MSK indications (with CTSI) had previously undiagnosed RVD-axSpA who may be identified using a validated CT screening tool.

This project is a testament to potential referral strategies for undiagnosed IBD patients with suspected axSpA in modern

medical practice. This can supplement the secondary care referral strategies to identify undiagnosed axSpA, thereby reducing diagnostic delay further and allowing early access to treatment (see Figure 11).

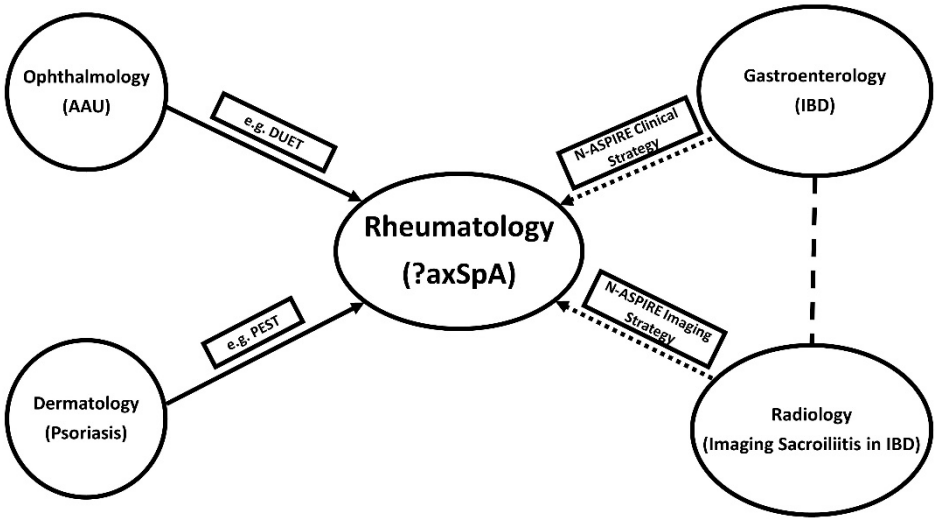

Figure 11: Referral Strategies.

Figure by author. AAU: acute anterior uveitis; axSpA: axial spondyloarthritis; DUET: Dublin Uveitis Evaluation Tool; IBD: inflammatory bowel disease; PEST: Psoriasis Epidemiology Screening Tool

5.2 Critical Appraisal of Project

In retrospect, there are elements of the project which could be improved. I will discuss these points in the next few paragraphs.

5.2.1 Development of a clinical tool

Given the design of the N-ASPIRE Clinical Strategy Study, it is possible that one could envision recruiting more patients into the study to enable the formation of two cohorts, a developmental cohort, and a validation cohort. One could use the developmental cohort to establish the prevalence of undiagnosed axSpA verified by a rheumatology in IBD patient attending routine secondary care IBD clinics. Following which, the characteristics of the undiagnosed axSpA versus the non-axSpA group could be used to explore any significant variables. By using logistic regression, one may be able to uncover key variables in the clinical referral strategy that could constitute a clinical referral tool which can subsequently be tested in the validation cohort. In this way, the clinical referral strategy would be proven more robustly.

In the current study, we approached 470 patients to find 82 patients (17%) for a full clinical and imaging assessment which resulted in 4 undiagnosed cases. As this was a low event rate, there would be a low permutation of outcomes, thus the increase in a single event or not will greatly influence the test statistics during statistical testing, leading to erroneous conclusions.

Ideally, we could have greatly increased the number of patients recruited into the study, but this would be beyond the time and

budget allocated for this study. On reflection, the task of developing a clinical referral tool in IBD patients will more likely be a national level project with contribution from multiple research sites to increase sample size and thus the event rate.

5.2.2 Assessment of non-axSpA subjects

In the clinical study, we should have assessed all 51 patients without self-reported chronic back pain instead of trying to match one patient for every two patients with self-reported chronic back pain, because eventually there were only 10 patients who were not selected for clinical assessment. This then led to difficulty in trying to perform conclusive statistical analysis on this group due to the unknown data of the missing subjects and matching.

There were ethical and financial constraints in trying to assess all the patients. Also, we would be unlikely to gain further knowledge, especially in a group who has self-reported to be asymptomatic for chronic back pain. In our sample, there was a single undiagnosed "asymptomatic" patient with axSpA. This patient admitted to the presence of chronic lower back pain on further detailed questioning during the clinical assessment, but this symptom was not reported on the self-reported questionnaire by the patient due to personal health belief.

In the imaging study, apart from the (33/60) 55% who did not complete or decline to participate, we were unable to justify, for ethical reasons, contacting and assessing the other 241/301 (80%) who had their CT scans for non-musculoskeletal reasons especially when there were no imaging changes on CT. In an ideal word, it

would be interesting to understand if there were any back symptoms in these patients, as we know that CT changes are usually present after having undiagnosed axial inflammation for a prolonged duration. These patients who are symptomatic may have undiagnosed axSpA. We hope that for these patients, the clinical strategy will be the one that picks up these symptomatic patients either in secondary care IBD clinics or via primary care.

5.2.3 Screening of axSpA using MRI scans vs CT scans used for IBD assessment

During the time of development of the imaging study, the MRI protocol used for diagnosis of axSpA and IBD disease assessment was very different. It is of common knowledge that although MRI will eventually be the preferred modality for the assessment of inflammatory gut disease, the use of CT scans in acute presentations of inflammatory bowel disease and other acute situations still exceeds the use of MRI scanning [147–150]. At the time of development, there were also recent studies by Chan et al [116,117] who developed a practical screening tool using CT scans and suggested that it could be used to screen for axSpA patients in IBD patients. Thus, we used CT as the imaging modality in our imaging strategy study instead. Moving forward in time, Evans et. al. under the expert guidance of the late Deepak Jadon [151], have tried to show the use of magnetic resonance enterography (MRE) as a screening tool to identify axSpA that have been clinically diagnosed with a sensitivity of 60% and specificity of 85%. They concluded that due to the poor sensitivity, the use as a screening tool is limited.

5.3 Updates from the passage of time

An editorial [112] and two recent articles [152,153] after the completion of this project have echoed and agreed with the concepts discussed in this thesis including: the difficulty in differentiating axSpA and IBD related disease; the lack of consensus in definitions and the variability in the current reported data in this field; the importance of joint working between other specialties and rheumatology; the delay in diagnosis in axSpA being an ongoing problem; and the need for robust evaluation of simple non-burdensome referral strategies to improve diagnostic delay in axSpA. The whole project team was also delighted that the work has been incorporated into a national report [154] that was produced by the National Axial Spondyloarthritis Society (NASS) on IBD and axSpA. In June 2023, NASS, in collaboration with Crohn's & Colitis UK and with support from the British Society for Gastroenterology (BSG), launched the findings of their landscape review into diagnosing axSpA in people living with inflammatory bowel disease. This is part of their "case for change" reports, where they provide resources to reduce time to diagnosis in axSpA for healthcare professionals and the wider health ecosystem in the United Kingdom to reduce time to diagnosis in axSpA. They have noted the prevalence rates of chronic back pain (19%) and undiagnosed axSpA (5%) in IBD patients from our study and will be working further to estimate the health economics around the increased referral burden to rheumatology. In addition, they also recommended a gold standard referral pathway for the referral of

IBD patients with suspected axSpA, which is not dissimilar from our proposed clinical referral strategy (see Figure 12).

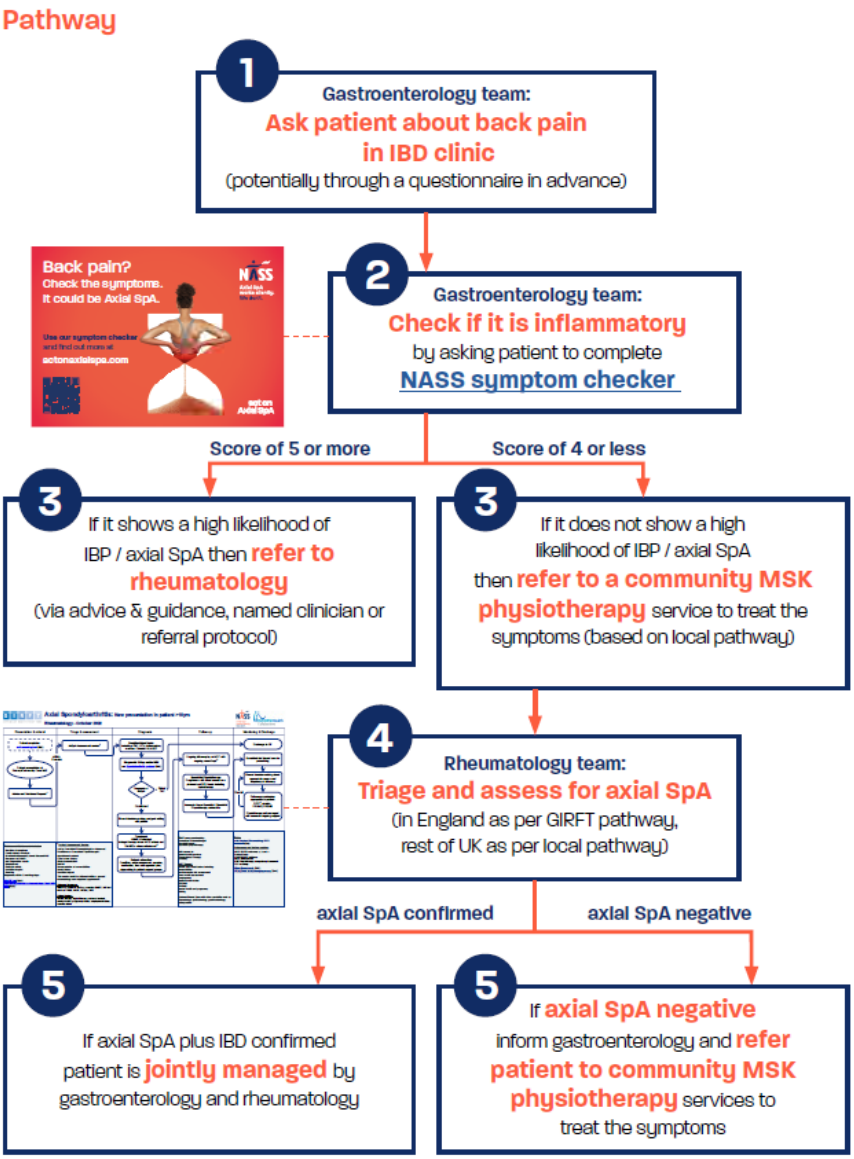

Figure 12: NASS IBD referral pathway.

This is taken from the NASS document. DOI: https://www.actonaxialspa.com/wp-content/uploads/2023/06/5620-NASS-IBD-in-diagnosis-of-AS_Digital.pdf

5.4 Future directions

The results and frameworks from this project are unlikely to be the final stop, it is likely to be the beginning of a journey. Given the many challenges around the axSpA related IBD spectrum disease, there is a need for further research into the following:

- Improving and building on the results and referral strategies frameworks from this project, and to design a simpler and effective referral strategy.
- Developing and validating a clinical referral tool based on the refined referral strategy, so that each referral is more specific and targeted. This will reduce overall health economics.
- Identifying and improving the understanding of the characteristics of axSpA-related IBD spectrum disease from the cohort of referred patients.
- Exploring if there are any similarities or differences between axSpA-IBD populations vs isolated IBD or axSpA populations.
- With a more defined patient cohort, further exploration of treatment and management strategies can be formulated and tested.
- Ultimately the programme of research should ideally result in a consensus in terminology, classification, referral strategies, diagnosis, and management. Further clinical science projects using molecular genetics, GWAS hypothesis free testing and artificial intelligence, may elucidate the pathophysiology of the axSpA related IBD spectrum diseases.

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Appendix

1. Protocol of the N-ASPIRE Clinical Strategy Study

Our Vision To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS Foundation Trust

University of East Anglia

N-ASPIRE Tool Protocol	
Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - Axial SPa Ibd REferral Tool (N-ASPIRE Tool)] N-ASPIRE Tool	
Chief Investigator	Dr Chong Seng Edwin Lim MBBS, MRCP (UK) (Rheumatology) Senior Research Fellow (Post-CCT) Norfolk and Norwich University Hospital
Support / Funder	National Ankylosing Spondylitis Society (NASS) NNUH Rheumatology Department
Sponsor	Norfolk & Norwich University Hospital NHS Foundation Trust (NNUH) – Lead Sponsor University of East Anglia (UEA) – Co-sponsor
Document type	Final protocol
Version number	2.0
Date	3rd May 2018
This protocol does not have regard to the HRA guidance and order of content	

Protocol Version

Document type	Version No.	Version Date	Person	Reason
Final	1.0	01/03/18	Dr CSE Lim	Initial
Final	2.0	01/05/18	Dr CSE Lim	Post REC changes

Research Reference Numbers

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Support / Funder Reference Number	N/A
IRAS Project ID Number	223356
REC Reference Number	18/EE/0102
International Standard Randomised Controlled Trial Number (ISRCTN)	ISRCTN30265575 https://doi.org/10.1186/ISRCTN30265575

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List of Abbreviations & Definitions

AAU	Acute Anterior Uveitis
AP	Anteroposterior
AS	Ankylosing Spondyloarthritis
ASAS	Assessment of Spondyloarthritis International Society
axPsA	Axial Psoriatic Arthritis
axSpA	Axial Spondylcarthritis
AS	Ankylosing Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASG	Bath Ankylosing Spondylitis Global score
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body Mass Index
CBP	Chronic Back Pain
CCT	Certification of Completion of Training
CD	Crohn's Disease
CI	Confidence Interval
CI	Chief Investigator
CORE	Fighting Digestive Diseases
CRF	Case report form
CRP	C reactive protein
CT	Computer Tomographic / Computer Tomography
CTIMP	Clinical Trial of an Investigational Medicinal Product
Dx	Diagnosis
EAM	Extra-Articular Manifestations
ESR	Erythrocyte Sedimentation Rate
ESSG	European Spondyloarthropathy Study Group
GCP	Good Clinical Practice
GP	General Practitioner
HLA-B27	Human Leucocyte Antigen B27
IBD	Inflammatory Bowel Disease
IBP	Inflammatory back pain
MST	Multi-Specialist Team
mNYC	Modified New York Criteria
MRI	Magnetic Resonance Imaging
NASS	National Ankylosing Spondylitis Society
NHS	National Health Service
NNUH	Norfolk & Norwich University Hospital
nr-axSpA	non-radiographic axial spondyloarthritis
NSAIDS	Nonsteroidal Antiinflammatory Drugs
PCF	Participant Consent Form
PI	Principle Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PROMS	Patient report outcome measures
PsSpA	Psoriatic Spondyloarthropathy/Spondyloarthritis
PVD	Physician Verified Diagnosis
R&D	Research and Development
rad-axSpA	Radiographic Axial Spondyloarthritis
RDS	Rheumatologist Diagnosis Sheet
REC	Research Ethics Committee
SIJ	Sacroiliac joint
SNAC	Screen Negative Assessment Control
SpA	Spondyloarthritis / Spondyloarthropathy
SOP	Standard Operating Procedure
SQ	Screening Questionnaire

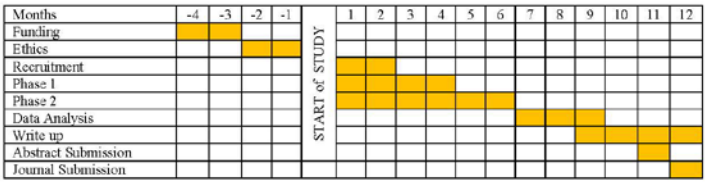
TNF	Tumour Necrosing Factor
W/O	Without
X-ray	Radiograph / Radiographic
UC	Ulcerative Colitis

List of Definition of Terms

Vasovagal reaction	A reflect reaction to a stimulus like having a blood test, which cause dilatation of your peripheral vessels leading to a drop in the blood pressure causing dizziness and fainting.

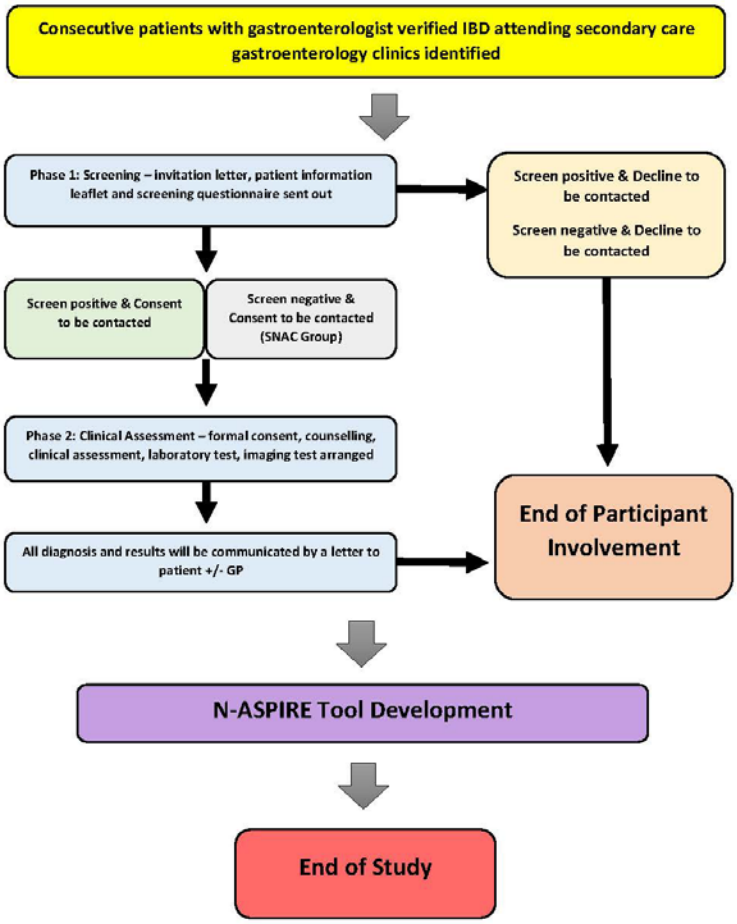
Table of Contents

1 Study Summary

Title	Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - axial SpA IBD referral Tool (N-ASPIRE Tool)]
Acronym	N-ASPIRE Tool
Study aims and objectives	• To estimate the prevalence of physician verified axSpA in an IBD population and identify undiagnosed cases as the "hidden burden" of axSpA. • The assessment of these subjects' characteristics will facilitate the development of a referral tool that can aid clinicians to improve identification, reduce diagnostic delay and enable access to treatments.
Study Design	Investigator led, cross-sectional, single centre study
Study Site	Norfolk & Norwich University Hospital
Study Duration	12 months from study commencement date
Study Timeline	
Sample Size	390 subjects (minimum number needed to be screened)
Study Population	Adults aged 18-80 with physician verified IBD who are not on biologic treatments and have chronic back pain onset younger than 45 years old
Primary outcomes	• Minimum prevalence of physician verified diagnosis of axSpA in IBD subjects • Minimum prevalence of undiagnosed axSpA in IBD subjects • Establish the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, diagnostics odd ratio of the N-ASPIRE Tool
Secondary outcomes	• Minimum prevalence of CBP in IBD subjects • Minimum prevalence of inflammatory back pain (via Calin, Berlin and ASAS criteria) in IBD subjects • Minimum prevalence of ASAS classified axSpA (clinical vs nr-axSpA vs AS) in IBD subjects • Minimum prevalence of axial SpA via ESSG criteria in IBD subjects • Minimum prevalence of AS via mNYC criteria • Minimum prevalence of symptomatic sacroiliitis (without a physician verified diagnosis of axSpA) • Quantity, type, frequency and duration of use of NSAIDS in IBD subjects with CBP • Prevalence of HLA-B27 in the above categories • Minimum prevalence of arthritis, enthesitis, dactylitis in IBD subjects with axSpA • Minimum prevalence of asymptomatic sacroiliitis (in IBD subjects without CBP) • Difference between the characteristics of subjects: IBD with CBP vs IBD without CBP • Difference between the characteristics of subjects: IBD with axSpA vs IBD with CBP but no axSpA diagnosis vs IBD without CBP or axSpA diagnosis • Difference between the characteristics of subjects: IBD with axSpA vs IBD without chronic back pain • Difference between the characteristics of subjects: IBD with axSpA vs IBD without axSpA

1.1 Study Overview Flow Chart

Figure 1 – Study Overview Flow Chart



2. Introduction

2.1 Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis predominantly involving the spine and sacroiliac joints, with or without extra-spinal musculoskeletal manifestations (peripheral arthritis, enthesitis, dactylitis) and extra-articular manifestations (iritis / anterior uveitis, psoriasis and inflammatory bowel disease) (1). AxSpA has a disease spectrum. This includes *non-radiographic axSpA* – individuals with axSpA features but without established radiographic changes, and *radiographic axial spondyloarthritis* (commonly known as Ankylosing Spondylitis) – individuals with axSpA features and radiographic sacroiliitis (2).

AxSpA is diagnosed clinically based on suspicious clinical features supported by laboratory tests (Human Leucocyte Antigen B27, raised C reactive protein) and imaging (Magnetic Resonance Imaging and/or X-ray). Advances in MRI have enabled earlier diagnosis of axSpA via the identification of bone marrow oedema compatible or highly suggestive of axSpA in the sacroiliac joints and/or spine prior to the development of structural changes on radiographs (3–7). Classification criteria for axSpA (see Figure 2) based on a combination of imaging or clinical criteria in patients with chronic back pain with onset before 45 years of age has been developed by the Assessment of SpondyloArthritis international Society (8,9). These are useful for research purposes but are not diagnostic criteria.

Figure 2 – ASAS Classification Criteria for Axial Spondyloarthritis (axSpA) (9)

<table>
<tr><td colspan="3">In patients with ≥ 3 months of back pain and age at onset < 45 years old</td></tr>
<tr><td>Sacroiliitis on imaging * AND
≥1 SpA feature**</td><td>OR</td><td>HLA-B27 AND
≥2 other SpA features **</td></tr>
<tr><td colspan="2"><u>** SpA features:</u>
• Inflammatory back pain
• Arthritis
• Enthesitis (heel)
• Uveitis
• Dactylitis
• Psoriasis
• Crohn's/Colitis
• Good response to NSAIDS
• Family history for SpA
• HLA-B27
• Elevated CRP</td><td><u>* Sacroiliitis on imaging:</u>
• Active acute inflammation on MRI highly suggestive of sacroiliitis associated with SpA
• Definite radiographic sacroiliitis according to modified New York criteria</td></tr>
</table>

Axial SpA typically begins in the 2nd and 3rd decade (10). Delay to diagnosis is a major problem with an average delay of between 8-10 years. This means that patients often endure intolerable symptom, linked to worse outcomes (disease activity, function, radiographic), despite the availability of effective new therapies (11). Early treatment offers the best chance of drug free remission and early disease responds best to TNF inhibitors (12,13). Sykes et al

(14) have recently shown that the delay to diagnosis has not improved despite the advances in modern imaging and new approaches to diagnosis. They divided 1193 patients with a physician-verified diagnosis of axSpA into a historical (diagnosed pre-2009) and current cohort (diagnosed 2009-2013) and found that the average delay to diagnosis in the historical cohort was 8.53 years, and 9.39 years in the current cohort. They concluded that there is still a need for further targeted education of health-care professionals in order to address the issue of delay to diagnosis. National Ankylosing Spondylitis Society (NASS), the only charity in the United Kingdom dedicated to supporting patients with axSpA, concluded in a recent conducted survey of axSpA patients that the average delay to diagnosis (onset of symptoms to diagnosis) is still 8.50 years (15).

In an attempt to address the problem of delay to diagnosis, the National Ankylosing Spondylitis Society has developed the "BACK PAIN PLUS" campaign which is an awareness campaign targeted at secondary care specialist who manage patients with common extra-articular manifestations of axSpA: acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis. It is proposed that these patients should be screened for the presence of chronic back pain (with inflammatory features) and referred to rheumatology if they are found to screen positive (16).

As mentioned earlier, axSpA is associated with extra-articular manifestations such as AAU, IBD and psoriasis. The estimated range of prevalence of AS in IBD patients is 1% to 25%, with a recent calculated pool prevalence of 3% (17). The prevalence range varies considerably and is reported to be between 4% to 7% in axSpA (18,19). Radiographic sacroiliitis (symptomatic and asymptomatic) is common, reported to be prevalent in IBD patients between a range of 1% to 45% (20) with a recent calculated pool prevalence of 10% (17). It has been shown that about 4% of patients with IBD presents before the diagnosis of AS and twenty years later these percentages doubled to about 7.5% while the risk of developing IBD in patients with AS when compared with the general population is increased by 3.3-fold (21) (22). In addition, there is increasing evidence from genome-wide association studies that there is a relationship between AS and gut inflammation which may explain the close association of the two conditions. Shared genetics may contribute to a common inflammatory pathway (23,24).

Referral strategy trials have been proposed to facilitate identification of axSpA but almost all are primary care referral strategies based on a combination of inflammatory back pain, imaging findings, HLA-B27 results and associated clinical features (4,25–27). In secondary care referral, Haroon et al have recently developed an algorithm to direct AAU referrals to rheumatology (28). Also, Gotler et al and Leclerc-Jacob et al have both shown that 9.1% to 16.7% of IBD patients have MRI sacroiliitis (as defined by the ASAS Classification Criteria) but no co-relation with a clinical verified diagnosis of axSpA (29,30) has been reported.

2.2 Rationale

We propose that it is important to understanding the prevalence of physician verified axSpA in the IBD population (with the aid of contemporary imaging technologies such as MRI) as the undiagnosed cases may represent a "hidden burden" of axSpA. This will then allow the assessment of their characteristics to facilitate the development of a referral tool to improve identification, thereby reducing the diagnostic delay and enable the access to available effective treatments.

3. Aims and Objectives

3.1 Aims

A single centre prospective observational estimation of the prevalence of undiagnosed axial spondyloarthritis in existing secondary care inflammatory bowel disease population and the development of a referral tool to facilitate earlier detection.

3.1 Objectives

Stream 1:

- To estimate the prevalence of physician verified axial spondyloarthritis in inflammatory bowel disease.
- To estimate the prevalence of undiagnosed physician verified axial spondyloarthritis in inflammatory bowel disease – the "Hidden Burden" of disease.

Stream 2:

- To develop a referral tool for detection of undiagnosed axial spondyloarthritis in inflammatory bowel disease patients – the N-ASPIRE Tool.

3.1 Primary Outcomes

Stream 1:

- Minimum prevalence of physician verified diagnosed axSpA in IBD subjects (See Figure 4 – Statistics Flow Chart in Section 7. Statistical Methods)
- Minimum prevalence of undiagnosed physician verified diagnosed axSpA in IBD subjects

Stream 2:

- Establish the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, diagnostics odd ratio of the N-ASPIRE Tool

3.2 Secondary Outcomes

Stream 1:

- Minimum prevalence of CBP in IBD subjects
- Minimum prevalence of inflammatory back pain (via Calin, Berlin and ASAS criteria) in IBD subjects
- Minimum prevalence of ASAS classified axSpA (clinical vs nr-axSpA vs AS) in IBD subjects
- Minimum prevalence of axial SpA via ESSG criteria in IBD subjects

- Minimum prevalence of AS via mNYC criteria
- Minimum prevalence of symptomatic sacroiliitis (without a physician verified diagnosis of axSpA)
- Quantity, type, frequency and duration of use of NSAIDS in IBD subjects with CBP
- Prevalence of HLA-B27 in the above categories
- Minimum prevalence of arthritis, enthesitis, dactylitis in IBD subjects with axSpA
- Minimum prevalence of asymptomatic sacroiliitis (in IBD subjects without CBP)
- Difference between the characteristics of subjects: IBD with CBP vs IBD without CBP
- Difference between the characteristics of subjects: IBD with axSpA vs IBD with CBP but no axSpA diagnosis vs IBD without CBP or axSpA diagnosis
- Difference between the characteristics of subjects: IBD with axSpA vs IBD without chronic back pain
- Difference between the characteristics of subjects: IBD with axSpA vs IBD without axSpA

4. Study Design

4.1 Study description

N-ASPIRE Tool will include two design streams with complementary methodology.

Stream 1: A cross-sectional survey of patients with IBD in secondary care, supplemented by a structured assessment of a subset of participants (to include those with and without chronic back pain).

Stream 2: An evidence-based development of a referral tool to facilitate earlier detection of undiagnosed axial spondyloarthritis in IBD patients with chronic back pain: the N-ASPIRE Tool (Norfolk - Axial SPa Ibd REferral Tool)

Stream 1 will consist of two phases outline below (Section 4.1.1 to 4.2). Stream 2 only consist of data analysis and will be described in Section 7.3.

4.1.1 Phase 1: Screening

Recruited subjects meeting the inclusion criteria for phase 1 (See Section 5.1) are sent an invitation package. The SQ is a modification of a validated questionnaire by Hamilton et al (31).

The invitation package contains:

1. Invitation cover letter by the gastroenterology team (See Appendix A)
2. Participant Information Sheet (PIS) (See Appendix C)
3. Screening Questionnaire (SQ) (See Appendix F)

4. NNUH Plain X-ray Patient Information (See Appendix I)
5. NNUH Magnetic Resonance Imaging (MRI) Patient Information (See Appendix J)

A second invitation letter is sent out after one month. A prepaid return envelope will be provided with the invitation package.

4.1.2 Phase 2: Clinical assessment

The following subjects will be invited to attend a clinic appointment at the rheumatology department for clinical assessment:

1. Screen POSITIVE subjects: All subjects who have completed phase 1 and meet the inclusion criteria for phase 2 (See Section 5.2) will then be invited to attend a clinic appointment at the rheumatology department for clinical assessment if they have given consent to be contacted in the screening questionnaire.
2. Screen NEGATIVE subjects: A sample [Screen Negative Assessment Control (SNAC) Group] from the control group (IBD subjects without chronic back pain) will be selected for clinical assessment. These are the first X consecutive subjects who have completed phase 1 and *do **not** meet the inclusion criteria for phase 2* will be invited to attend a clinic appointment at the rheumatology department for clinical assessment if they have given consent to be contacted in the screening questionnaire. X will be in a ratio of 1:2 screen positive subjects. The sample will be age and sex matched to the first X consecutive screen positive subjects.

Formal consent will be obtained at the clinic appointment. Clinical assessment will include a structured history, structured physical examination and rheumatological outcome measurements using a paper Case Report Form (CRF). Laboratory test will include HLA-B27, CRP and ESR using the trust's standard routine pathology protocol. Imaging studies will include an anterior-posterior radiograph of the sacroiliac joints and MRI using the trust's standard X-ray and axSpA imaging protocol respectively.

A physician verified diagnosis (PVD) will be made via virtual Multi-Specialist Team (MST) meetings. The final PVD and results of the investigations will be communicated to the patient and their GP if consent have been previously given, their trial involvement will then end.

Participants will receive reimbursement for reasonable travel expenses (based on car mileage or train/bus ticket) up to a maximum of £10 pounds per participant per visit. No additional payments or incentives above the travel expenses will be offered.

Subjects who are unable to complete the Clinical assessment, Laboratory test or MRI will be will not continue with Phase 2. A letter communication will be sent to the patient and their GP if consent have been previously given, and their trial involvement will then end.

Subjects who have completed phase 1 and do not meet the inclusion criteria for phase 2 will have their data included in the control group if consent was given in their screening questionnaire. All subjects NOT invited for a clinical assessment will be sent a letter of appreciation (See Appendix B) and their study involvement will then cease.

4.1.3 Imaging Protocol

The technical language of the trust's standard imaging protocol for anterior-posterior radiograph of the sacroiliac joints is "*Subject supine on the table with legs internally rotated, Fixed Focal Distance (FFD) 115 cm, image to include crests superiorly, both greater trochanters laterally and proximal femur inferiorly*".

The technical language of the trust's standard imaging protocol for MRI axSpA protocol is "*Sagittal T1 Lumbar(L)-spine, Sagittal T2 Fatsat L-spine, Axial T2 L-spine as appropriate, Sagittal T1 Thoracic(T)-spine, Sagittal T2 Fatsat T-spine, Axial T2 T-spine as appropriate, Coronal oblique T1 SIJ, Coronal oblique T2 Fatsat SIJ*".

4.1.4 Pregnancy Safety Screening

A subject will be screened for the possibility of pregnancy throughout the study.

If a subject is eligible for Phase 2 of the study, the subject will be asked about the possibility of pregnancy during the telephone contact. If unable to provide a verbal confirmation that there is no chance of pregnancy, then the patient will not proceed with Phase 2. A letter of appreciation will be sent out to them and their study involvement will end.

During the consent process, a subject will be asked again about the possibility of pregnancy. If unable to provide a verbal and written confirmation that there is no chance of pregnancy, then the patient will not proceed with Phase 2. A letter communication will be sent to the patient and their GP if consent have been previously given, and their trial involvement will then end.

During imaging studies, radiology staff will follow their routine imaging policy:

- If female subject aged 12-55 is able to confirm that there is no chance of pregnancy than the radiographer will proceed with the X-ray examination.
- If they are unsure, they will discuss their last menstrual period (LMP); if the imaging is within 28 days of their last LMP the radiographer will proceed with the X-ray examination.
- As this will be a research imaging requirement rather than a clinical requirement, the radiographer will postpone the X-ray examination and discuss with the research team if any doubt arises.
- There has been no reported effect from MRI to the unborn child, but the above general rule should also be followed.

All patients unable to complete the study imaging due to the above pregnancy safety concerns will not continue with Phase 2. A letter communication will be sent to the patient and their GP if consent have been previously given, and their trial involvement will then end.

4.1.5 Assessment of the SNAC Group

A minimum sample of IBD patients without chronic back pain will be selected and assessed. This group is known as the Screen Negative Assessment Control (SNAC) Group. AxSpA typically presents with a history of chronic back pain (32) but there is evidence of asymptomatic sacroiliitis in patients with IBD (33), who have MRI results similar to that of axSpA (29). It is therefore important to understand the underlying frequency of this phenomenon in our population to serve as a baseline frequency.

To ensure that those volunteering to participate in this group is well informed, they are initially contact by telephone by an investigator before given a clinical appointment. They will be made aware that they are in the screen negative group but are eligible for a clinical assessment and further investigations. It will be explicit that their participation is voluntary and under routine care a screening assessment will not normally be performed as the clinical significance of positive findings (if present) in their assessments is not known without the symptom of chronic back pain.

If they wish to participate and give informal consent to a structured history, structured physical examination, rheumatological outcome measurements, laboratory test and MRI, a formal invitation for clinical assessment will be given subsequently.

Formal consent and further counselling will be obtained and conducted at the clinic appointment. Clinical assessment will be performed as above protocol in Section 4.1.2 *without* an anterior-posterior radiograph of the sacroiliac joints as the risk of exposure to radiation likely to be ethically unacceptable in this group.

4.1.6 Treatment of results

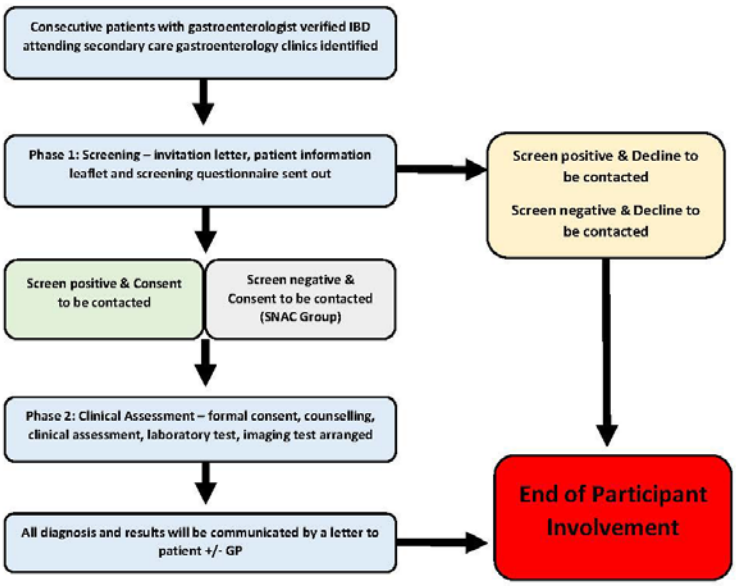
All results will be treated as "real world" routine clinical practice. HLA-B27 status is either positive or negative as provided in the lab report. CRP and ESR are abnormal if they are outside the laboratory reference range. The sacroiliac joints radiography and MRI of the sacroiliac joints and spine using the NNUH axSpA protocol will be read/supervised by a musculoskeletal radiologist with appropriate experience and reported as per routine clinical practice. Any discrepancies will be discussed in a weekly radiology multidisciplinary meeting and agreement will be by a consensus majority. Grading of radiographic sacroiliitis of the sacroiliac joints is made according to guiding reference to grading according to the modified New York criteria (34), while a positive sacroiliac joint MRI for inflammation is made according to guiding reference with the ASAS-OMERACT 2009 definition (7) with its recent update and guidance (6). A positive spinal MRI for inflammation is made according to guiding reference with the ASAS-OMERACT 2012 definition (35).

4.1.7 Physician verified diagnosis of axSpA

Each subject will be discussed in a virtual Multi-Specialist Team (MST) meeting before and after the laboratory and imaging results. The MST will be made up of a panel of 3 rheumatologist of varying experience (post-CCT research fellow, junior consultant and senior consultant) to simulate real world situation. Clinical data for each patient will be presented as per "raw data" collected in the CRF. After discussion of the clinical data, each rheumatologist will make either a positive or negative diagnosis of axSpA and indicate the level of confidence of the diagnosis on a 10 point Likert scale on the Rheumatologist Diagnosis Sheet (RDS; See Appendix H). The definition of a PVD in this study is when a positive axSpA is made in 2 of 3 rheumatologist and the level of confidence will be reflected by the average of the three Likert scale. A similar process will follow when the results of imaging and laboratory results are made known to them. Any discrepancy between the before and after investigation revelation PVD will be re-discussed in the MST and a final PVD made by a majority consensus vote of 2 of 3 rheumatologist. An alternative diagnosis will be suggested if possible when no final PVD of axSpA is made.

4.2 Stream 1 FLOW CHART

Figure 3 – Stream 1 Flow Chart



5. Study Population

The study population will be consecutive patients attending secondary care gastroenterology outpatient clinics in a single university hospital (NNUH).

5.1 Inclusion criteria for Phase 1 (Screening)

- Gastroenterologist verified diagnosis of inflammatory bowel disease (Crohn's disease or Ulcerative colitis, with either endoscopic, radiological or histological evidence of disease based on established criteria(36))
- Age ≥ 18 and ≤ 80 years old
- Patient willing and able to participate in the study
- Including known/previous diagnosis of AS or axSpA

5.2 Inclusion criteria for Phase 2 (Clinical assessment)

- Chronic back pain (≥ 3 months)
- Onset of back pain before 45 years old
- Including known/previous diagnosis of AS or axSpA (if unable to verify diagnosis retrospectively)

5.3 Exclusion criteria

- Any type of biologic therapy for (previous or current) treatment of IBD (the reason being the effects of biological therapies on the natural course of axSpA is still unknown (37), thus the inclusion of these subjects would bias the study findings)
- Unable to tolerate MRI scanning (e.g. current history of claustrophobia) or contra-indication to MRI scanning (including but not limited to e.g. pacemaker, pregnancy, metallic or conducting foreign body, etc.)
- Age <18 or >80 years
- Patients lacking in capacity and/or unable to give informed consent
- Patients unable to understand English to sufficient degree to be able to complete a questionnaire
- Illiteracy
- Prisoners
- Patients unwilling to take part in the study

6. Recruitment and Enrolment

6.1 Identifying participants

Consecutive patients attending secondary care gastroenterology clinics with the following characteristics are identified as potential subjects for the study:

- Gastroenterologist verified diagnosis of IBD (CD or UC)
- Not on biologic therapy for IBD
- Regardless of IBD activity
- Regardless of known previous diagnosis of AS/axSpA

6.2 Screening participants

Eligible patients for Phase 1 will be sent a screening questionnaire (which is part of the invitation package). The completed screening questionnaire will be returned via a prepaid return envelope included with the invitation package. If the patient declines to participate in the study, they will be encouraged to return the screening questionnaire, so that they wish are respected and a second reminder letter will not be sent out to them.

If the patient meets the eligibility criteria (See Section 5), and has given written consent to be contacted for Phase 2, they will be contacted via telephone by the researcher and a clinic appointment at the rheumatology department will be arranged. If the patient meets the eligibility criteria (See Section 5), and has declined to be contacted for Phase 2, a letter of appreciation will be sent out to them and their study involvement will end.

If the patient does not meet the eligibility criteria (See Section 5), and has given written consent to be contacted for Phase 2, they will be contacted via telephone by the researcher and a clinic appointment at the rheumatology department will be arranged – if they are included in the SNAC Group. If the patient does not meet the eligibility criteria (See Section 5), and has given written consent to be contacted for Phase 2, a letter of appreciation will be sent out to them and their study involvement will end – if they are NOT included in the SNAC Group.

During any contact over the telephone, the screening of eligibility criteria (especially the exclusion criteria and pregnancy) will be check verbally before an appointment is offered. If there are any exclusion criteria present, the patient will not proceed with Phase 2. A letter of appreciation will be sent out to them and their study involvement will end.

6.3 Consenting participants

Every eligible patient will be sent a participant information sheet (PIS). They will be given approximately four weeks to review the information on the PIS (See Appendix C), which will contain the contact information for the study team should they have any queries.

The patient will be given the opportunity to indicate their wish to participate in the study by completing statements in the screening questionnaire (See Appendix F). They will give written consent to be contacted by the research team for Phase 2 of the study. They will also give written consent for data access and storage, and involvement of their GP. They will be considered to be enrolled in Phase 1 of the study on return of the screening questionnaire.

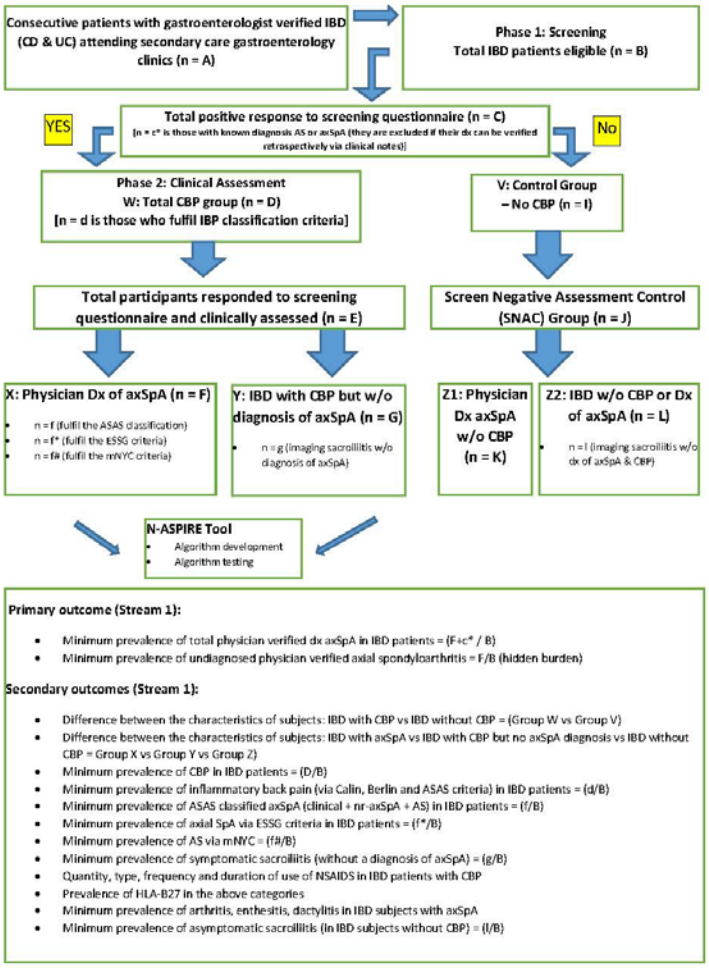
The participant who meet the eligibility criteria for both Phase 1 and Phase 2 (See Section 5) and have given permission to be contacted for Phase 2 (including selected subjects in the SNAC Group), will be contacted by the research team who will arrange a clinic appointment in the rheumatology department.

Formal written consent (See Appendix D) will be obtained at the clinic appointment after further discussion if needed. More time will be allowed if required by the participant to make the decision to take part in Phase 2 of the study. They will also indicate their consent to share their participation and results with their GP (See Appendix E).

7. Statistical Methods

7.1 Flow Chart

Figure 4 – Statistics Flow Chart



Primary outcome (Stream 1):

- Minimum prevalence of total physician verified dx axSpA in IBD patients = (F+c* / B)
- Minimum prevalence of undiagnosed physician verified axial spondyloarthritis = F/B (hidden burden)

Secondary outcomes (Stream 1):

- Difference between the characteristics of subjects: IBD with CBP vs IBD without CBP = (Group W vs Group V)
- Difference between the characteristics of subjects: IBD with axSpA vs IBD with CBP but no axSpA diagnosis vs IBD without CBP = Group X vs Group Y vs Group Z)
- Minimum prevalence of CBP in IBD patients = (D/B)
- Minimum prevalence of inflammatory back pain (via Calin, Berlin and ASAS criteria) in IBD patients = (d/B)
- Minimum prevalence of ASAS classified axSpA (clinical + nr-axSpA + AS) in IBD patients = (f/B)
- Minimum prevalence of axial SpA via ESSG criteria in IBD patients = (f*/B)
- Minimum prevalence of AS via mNYC = (f#/B)
- Minimum prevalence of symptomatic sacroiliitis (without a diagnosis of axSpA) = (g/B)
- Quantity, type, frequency and duration of use of NSAIDS in IBD patients with CBP
- Prevalence of HLA-B27 in the above categories
- Minimum prevalence of arthritis, enthesitis, dactylitis in IBD subjects with axSpA
- Minimum prevalence of asymptomatic sacroiliitis (in IBD subjects without CBP) = (l/B)

7.2 Power Calculation

The estimated prevalence of axSpA in IBD is assumed to be 5%. The power calculation based on the anticipated 5% prevalence with a confidence limits of ±0.05 would be 73 (E) subjects (See Figure 4). If it is assumed that only 75% will agree to participate in clinical assessment then 97.3 (D) subjects are needed to participate in Phase 2 of the study. Assuming that only 50% (38–40) will have CBP after screening then 194.6 (C) subjects will need to reply to the screening questionnaire. As the response rate to a postal questionnaire is typically around 50%, then 389.4 ≈ 390 (B) patients will need to be screened. Assuming that only 75% will be suitable for recruitment into the study after identification, then 518.9 ≈ 520 (A) minimum patients will be needed for an adequately powered study.

This study is feasible as personal communications with local IBD specialists reports an average attendance of 22 patients follow up per clinic per week in 2-3 specialised IBD clinics in NNUH from an estimated IBD population of 3500 patients in Norfolk.

In summary, the total minimum number needed to be screened from patients attending secondary care gastroenterology clinic is approximately 390 assuming the prevalence of axSpA in IBD subjects of 5%, with a confidence level of 95%.

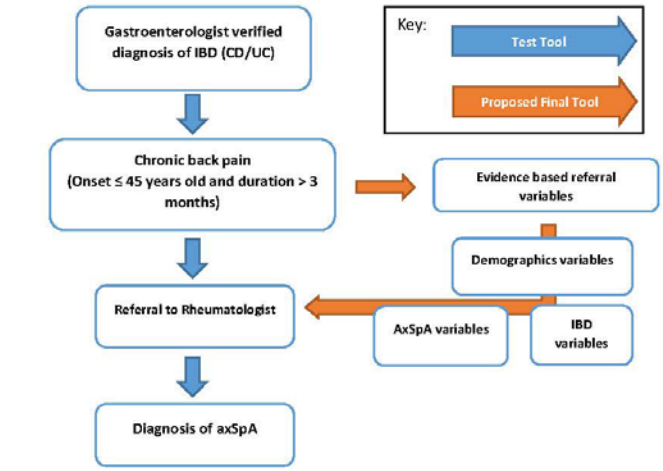
7.3 Proposed Analysis and N-ASPIRE Tool Development

For the calculation of prevalence of TOTAL and NEW axial spondyloarthritis (with known diagnosis of IBD), simple proportion/percentage of the frequency of those with the diagnosis to those without the diagnosis will be used (see Section 7.1, Figure 4).

Descriptive statistics will be used for patient characteristics, while difference in variables will be investigated using t tests for continuous variables and Chi-squared test and Fisher exact tests for categorical data. The association of different clinical variables with the diagnosis of axSpA will be determined using univariate and multivariate logistic regression analysis. Odd ratios and associated CIs will be used to measure the association between different variables. This evidence based will be used to inform and improve a test referral tool (Test Tool).

Efficacy of the test referral tool in predicting a diagnosis of axSpA will be measured in terms of sensitivity and specificity. Positive and negative predictive values including likelihood ratios and diagnostics odd ratio will also be determined. Further simple stepwise adjustment of the test referral tool will be undertaken with the view to improving its sensitivity and specificity, resulting in the production of the final referral tool (N-ASPIRE Tool) – See Figure 5.

Figure 5 – Test and N-ASPIRE Tool



Primary outcome (Stream 2):

- Establish the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, diagnostics odd ratio of the N-ASPIRE Tool

8. Funding

The study funding has been reviewed by the NNUH Research Office, and deemed sufficient to cover the requirements of the study.

NHS costs will be supported via NNUH and/or NNUH Rheumatology Department (F110 Patient Rheumatology Bone Fund in NNUH NHS Foundation Trust Charitable Fund (1048170))

The research costs for the study have been supported by National Ankylosing Spondylitis Society (NASS) and/or NNUH Rheumatology Department (F110 Patient Rheumatology Bone Fund in NNUH NHS Foundation Trust Charitable Fund (1048170)).

9. Data Collection and Management

9.1 Data collection, transfer, and recording

Data will be collected by research team, on paper forms which include the Screening Questionnaire (SQ), Case Report Form (CRF), and Rheumatologist Diagnosis Sheet (RDS). These will be supplemented with data from patient notes, electronic letters and electronic investigation results to complete any missing data if needed. The data collected will be entered onto an electronic Excel spread sheet. A full list is detailed below.

Screening Questionnaire (See Appendices F)

- Subject's details and consent:
  - Q1: Full name, date of birth, age, address, main contact number, gender
  - Q2: Statement – Decline to join the study
  - Q3: Statement – Consent to be contacted for Phase 2 of study
  - Q4: Statement – Consent to data access and storage
  - Q5: Statement – Involvement of General Practitioner
- Subject's previous diagnosis:
  - Q6: Statement – Previous diagnosis of AS or axSpA, with free text to provide further details
- Main questionnaire:
  - Q7: Question – Back pain last more than 3 months, with diagram to indicate site of pain
  - Q8: Question – Age of onset of back pain
  - Q9: Question – Mode of onset
  - Q10: Question – Radiation of pain to legs
  - Q11: Question – Alternating buttock pain

- Q12: Question – Night pain
- Q13: Question – Pattern of back pain/stiffness with time of day
- Q14: Choice – Time taken for improvement of back pain
- Q15: Question – Effect of exercise on back pain
- Q16: Question – Effect of rest on back pain
- Q17: Question – Effect of NSAIDS on back pain
- Q18: Question – Other musculoskeletal pain, with diagram to indicate site
- Q19: Choice – Indication of family history of associated axSpA conditions
- Q20: Choice – Previous personal history of associated axSpA conditions

- Brief Inflammatory Bowel Disease (IBD) questionnaire
  - Q21: Choice – type of IBD
  - Q22: Question – Age of symptoms onset and age of diagnosis by gastroenterologist
  - Q23: Question – Duration of IBD diagnosis
  - Q24: Choice – Current treatment for IBD, with area for free text
  - Q25: Choice – Previous surgery or hospitalisation due to IBD
  - Q26: Question – Participant description of current IBD activity
  - Q27: Question – Participant description of gastroenterologist impression of their current IBD activity

Case Report Form (See Appendices G)

- Section 1: Structured History
  - ITEM 1: Demographics & habits
  - ITEM 2: Description of back pain; Judgement on IBP
  - ITEM 3: Back pain pattern graph
  - ITEM 4: Details of axSpA associated conditions
  - ITEM 5: Other past medical history / Co-morbidity
  - ITEM 6: Allergies and current medications (including NSAIDS)
  - ITEM 7: Family History and Social History
  - ITEM 8: Any other relevant symptoms/history/notes
- Section 2: Structured Examination
  - ITEM 9: General Examination & BMI

- ITEM 10: 44 Swollen / 46 Tender Joint Count
- ITEM 11: Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- ITEM 12: Dactylitis Count
- ITEM 13: Tender points examination (41)

- Section 3: Rheumatological Outcome Measures
  - ITEM 14: BASMI (42), Chest expansion, Occiput-to-wall distance
  - ITEM 15: Patient report outcome measures (PROMS) – BASDAI (43), BASFI (44), BASG (45)
- Section 4: Gastroenterology Disease Activity Outcome Measures
  - ITEM 16: Disease Activity for Crohn's Disease – HBI (Harvey-Bradshaw Index) (46–48)
  - ITEM 17: Disease Activity for Ulcerative Disease – PMS (Partial Mayo Score) Disease Activity for Ulcerative Disease – PMS (Partial Mayo Score) (49–52)
- Section 5: Investigation Results
  - ITEM 18: Laboratory Results – HLA-B27, CRP, ESR
  - ITEM 19: Imaging Results – Radiograph of SIJ, MRI of SIJ and spine, MDT discussion notes
- Section 6: Diagnosis
  - ITEM 20: PVD of axSpA OR Alternative diagnosis
- Section 7: Classification (only when there is a PVD of axSpA)
  - ITEM 21: IBP Classification [Calin (53), Berlin (54), ASAS IBP criteria (55)]
  - ITEM 22: axSpA Classification [ESSG axSpA criteria (56), ASAS axSpA (9) criteria, mNYC AS criteria (34)]

Rheumatologist Diagnosis Sheet (See Appendices H)

- Is there a diagnosis axSpA before reviewing investigations (YES / NO) and Level of confidence (0 = not confident; 10 = very confident). Offer an alternative diagnosis if there is no diagnosis of axSpA (if possible).
- Is there a diagnosis of axSpA after reviewing investigations (YES / NO) and Level of confidence (0 = not confident; 10 = very confident). Offer an alternative diagnosis if there is no diagnosis of axSpA (if possible).

9.2 Data Management

During the study, any paper notes will be stored in study files in a room with restricted access. The data collected on paper (Screening Questionnaire, Case Report Form, etc.) will be transcribed to an Excel spreadsheet on NHS computers and stored on NHS Trust Network Drive with standard NHS information technology security and data management.

Identifiable data (Screening Questionnaire, Consent Forms, paper blood results and imaging results print out) will be stored separately from other study documents in a locked filling cabinet in a room with restricted access. Participants will be identified by a unique Participant Identification Number (PIN) for all other paper study documents. Only the linking documents (Screening Questionnaire and Consent Forms) will have both identifiable data and PIN. Participants' electronic data will be coded by a unique Data Number. Only an electronic Data Key will link the PIN and Data Number (i.e. electronic database). The electronic Data Key will be stored separately from the electronic database.

Access to collated participant data will be restricted to the Chief Investigator and/or appropriate qualified personnel from the research team. Computers used to collate the data will have limited access measures via user names and passwords. The accumulated electronic data will be analysed in a coded or anonymised manner.

Access to participants' personal/identifiable data may be required by appropriately qualified personnel from the research team (who may be different from those usually involved with the patient's care), sponsor company, the ethics committee and others responsible for overseeing research studies. This information is specified in the Patient Information Sheet, Screening Questionnaire and Patient Consent Form. Patients will give their written informed consent for the above personnel to have access to their data.

The storage and use of data after the end of the study will be describe in Section 16: Study Record Retention / Archiving. This section should also be read with Section 11.2: Good Clinical Practice – Confidentiality and Section 11.3: Data Protection.

10. Risk Assessment and Safety

10.1 Blood test

Blood tests have a wide range of uses and are one of the most common types of medical test. It is likely that a patient with IBD would have prior experience with blood test. The blood test may cause pain, bruising and rarely a vasovagal reaction. These adverse effects are normally short lived and reversible. Most subjects will normally experience some discomfort but will be accepting of this test.

10.2 Radiograph of sacroiliac joints

Current clinical guidance (57) still recommends conventional radiography of the sacroiliac joints as the first imaging method for the diagnosis of sacroiliitis (an imaging feature of axSpA).

Although inflammatory lesions seen on MRI is becoming a contemporary method for visualising early active sacroiliitis in axSpA, many patients with longstanding disease (which

may be as yet undiagnosed) may have diagnostic sacroiliitis on X-ray – hence the importance of doing X-ray first. In addition, the Modified New York criteria for the classification of Ankylosing Spondylitis (34) use an AP radiograph of the pelvis for grading of sacroiliitis. Due to the above prevailing evidence, we have also included an AP radiograph of the pelvis at part of the evaluation of suspected axSpA.

Radiographs will expose the subject to radiation and a radiograph of the pelvis has a typical effective dose of 0.7 millisievert which is equivalent to 4 months of natural background radiation. This has an estimated lifetime additional risk of fatal cancer per examination of 1 in 30,000 (58).

This risk will be communicated with the patient during the consent process. The patient may opt out of this investigation if they consider the risk unacceptable but will still be eligible to participate in the other aspects of the study. A standard NNUH Plain X-ray Patient Information leaflet will be provided to participant for more information (See Appendix I).

10.3 MRI Scans

MRI scans are safe and painless, although they can be uncomfortable – especially for some patients, lying still for long periods of time. The MRI scan using the trust axSpA protocol, will required the participant to be in the scanner for approximately 30mins. This is well within what is considered a tolerable period even for patients with known diagnosis of ankylosing spondylitis. Many patients will have previously experienced longer scan times, for e.g. whole-spine MRI or CT abdomen & pelvis.

In routine clinical diagnostic workup of a patient with suspected axSpA, MRI imaging will only be done if X-ray of the SIJ is normal or there is another reason preventing the use of X-ray. In this study, as the diagnostic process is compartmentalised so that the probability of a diagnosis can be considered by a virtual MST meeting before and after investigations, it is possible that subjects may be imaged with MRI scan even with a diagnostic X-ray. However, it should be balanced with the fact that in routine clinic practice, an MRI scan is also done usually at diagnosis to ascertain the activity and extend of the disease in order to plan prognosis and treatment.

Patients may be excluded from the study if they have contraindications to MRI, due to safety concerns – these are as per standard clinical practice, and are listed above (See section 5.3 Exclusion criteria). A standard NNUH MRI Patient Information leaflet will be provided to participant for more information (See Appendix J).

10.4 Incidental findings

Once a radiographer has completed the X-ray and MRI scan, the images will be reviewed by the local radiologist who will produce a clinical report. We would expect the clinical reports to be sent back to us within 2 weeks.

If the scans (or blood test) identifies something of clinical concern, the participant and their general practitioner will be notified as per usual NHS care (this will be highlighted in the Participant Information Sheet and Participant Consent Form). The patient's subsequent care will be directed by the participant's general practitioner.

10.5 Adverse Events and justification of non-reporting

An adverse event is any untoward medical event affecting a clinical trial participant. This is normally included in study protocols such as CTIMPs and observational studies where patients are reviewed sequentially. This study is a prospective, cross-sectional and non-interventional observational study. It is the observation of a symptomatic participant in a point interval in time utilising a single clinical visit with routine investigations as per standard of care (similar assessment would be done if they have been identified later via their general practitioner or specialist doctor). This information and adjunctive information through the postal screening questionnaire will help to decide on the probability of an undiagnosed associated condition in a patient already under routine primary/secondary care review. As such it is not feasible to adopt usual adverse event reporting procedures.

However, if any adverse events do occur within the confines of the study point interval (*this is liken to a routine NHS clinic appointment where clinical assessment is followed by a period of investigation leading to a possible diagnosis or no diagnosis*), and comes to our attention, the researchers will notified the patient's current responsible routine primary and/or secondary care teams to relay the any necessary information as per usual NHS care, so that further appropriate care for the patient can be planned, by their responsible physician.

Adverse events

The investigators agree with the Sponsor that non-serious adverse events will not be reported to the Trust R&D department because there is no intervention in this study. However, non-serious adverse events will be recorded by the researchers and must continue to be reported into the Trust's clinical risk systems, for example, adverse events which may occur during the normal routine procedures for the patient pathway i.e. during blood draw, x-ray and MRI.

Expected serious adverse events

The investigators agree with the Sponsor that this study is a prospective, cross-sectional and non-interventional observational study, where the focus of the study is to help to decide on the probability of detecting an undiagnosed associated condition in a patient already under routine primary/secondary care review. It is expected that this patient population may require hospitalisation, experience new medical problems and deterioration of existing medical problems. In recognition of this, events fulfilling the definition of a serious adverse event will not be reportable in this study. These events will be recorded by the researchers, but will not be subject to expedited reporting to the Research Ethics Committee (REC) but will be reported annually to the REC (in the annual progress report).

10.6 New diagnosis

Distress may be caused by receiving a letter in the post suggesting that their IBD diagnosis could be linked to another condition. The results of the assessment/scan could be distressing for some patients, if diagnosed with a new chronic condition. However, patients who are diagnosed with IBD are routinely given information from the charity CORE (59) by the gastroenterology team about their condition and they will be aware that inflammation in the gut may also trigger inflammation outside the intestine leading to arthritis, eye inflammatory or skin complaints (See Appendix K).

They should be relieved when they visit for the appointment and are assessed and investigated. The distress should be balanced against the benefits of an earlier diagnosis and potential treatment of their symptoms. This is highlighted in the Participant Information Sheet.

11. Good Clinical Practice

11.1 Ethical Conduct of the Study

The study will be conducted in accordance with the principles of good clinical practice.

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

11.2 Confidentiality

We will obtain study information from consented study participants. However, we will not undertake any of these activities during the identification of potential participants. The gastroenterology team (this is the direct healthcare team) will have a list of patients identified for recruitment with personal identifiable data. These patients will then be sent an invitation package to their home address. The returned Screening Questionnaire will contain personal identifiable information. By returning the questionnaire to the rheumatology department, the patient gives implied consent to the research team to know their details. The patient is then enrolled as a participant and a unique Participant Identification Number (PIN) will be issued. The signed Consent Form at the clinical assessment visit will also contain patient identifiable information with the linking PIN.

From this point onwards, all further data collecting physical forms (e.g. Case Report Form, Rheumatologist Diagnosis Sheet, etc.) will use the PIN instead of personal identifiable data. A Data Key will be used to convert the PIN to a Data Number. All electronic data will be coded using the Data Number instead of the PIN. The data collected on paper (Screening Questionnaire, Case Report Form, etc.) will be transcribed to an Excel spreadsheet. Further to this, the accumulated electronic data will be analysed in a coded or anonymised manner.

The researchers are contractually bound by their terms of employment to ensure that personal data remains confidential, in adherence with the NHS Code of Confidentiality. Identifiable data will only be held on patients who have given consent as this is a condition of entry into the trial. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

11.3 Data protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of

personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to the CI and appropriate study staff. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

12. Trial Management & Governance

12.1 General Management and Roles

The trial will be overseen by the Chief Investigator / Principle Investigator who will be responsible for the day-to-day management of the trial. He/she will co-ordinate all routine study procedures – in particular (a) ensuring that all ethics and research governance approvals are adhered to; and (b) training of investigators; and (c) responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the CI or delegated member of the study team. If the CI is not available the Co-Principle Investigator will take on the role of "acting CI".

The Principle Investigators will ultimately be responsible for the relevant clinical care of the participants for the duration of their participation. A study-specific delegation log (See Appendix L) will be prepared detailing the responsibilities of each member of staff working on the study.

12.2 Governance and Monitoring

The CI and PIs will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation. Monitors will be given access to the CRFs and database (on a read only) basis.

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

13. Training

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate curriculum vitae and training records (e.g. GCP training, See Training Log – Appendix P) will be maintained in the study files.

14. Insurance and Indemnity

Norfolk & Norwich University Hospital NHS Foundation Trust (NNUH) is the lead sponsor of the study. The University of East Anglia (UEA) is the co-sponsor. The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research. The University of East Anglia (UEA) hold insurance on the academic aspects of the study.

15. Protocol Amendments and Deviations

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study documents will not be implemented without these approvals.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be confirmed by the Sponsor. Both substantial and minor amendments will follow the submission and approval process outlined on the HRA website (https://www.hra.nhs.uk/approvals-amendments/amending-approval/). All amendments will be submitted to the research office(s) for approval before they are implemented. All staff working on the study will be updated of the approved amended documents and previous versions will be kept and marked as 'superseded' for reference.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

16. Study Record Retention / Archiving

The investigators agree to archive and/or arrange for secure storage of study materials in accordance with NNUH UEA SOP 900 – Storage and Retention of Research Documents. Documents/Data will be kept for a minimum of 5 years after the end of the study, including the identity of all participating patients (sufficient information to link records, Screening Questionnaire and original signed Participant Consent Form), to enable evaluations and/or audits from regulatory authorities.

Any paper data will be stored in a secured location with restricted access as determined by the Sponsor or, representatives of the Sponsor. Electronic data will be kept on the Sponsor's electronic data network with standard NHS information technology security. Access will be restricted to the Data Custodian or another appropriate person as determined by the Sponsor or, representatives of the Sponsor. Computers for access of the data will have limited access measures via user names and passwords.

Final study data set without any identifiable data or PIN or Data Number may be shared with the wider research community for ethically approved future studies when deemed appropriate by the Data Custodian or another appropriate person as determined by the Sponsor or, representatives of the Sponsor. This should be done in consultation with the Sponsor or, representatives of the Sponsor and should always conform to contemporary legal, ethical and regulatory framework including appropriate acknowledgement.

17. End of study

The participant's involvement in the study ends when they receive a final letter communicating the diagnosis and all relevant investigation results to patient (and GP) as describe in Section 4: Study Design. The patient's subsequent care will be directed by the participant's general practitioner. For patients who did not go through the clinical assessment, their active

participation will end when they receive the letter of appreciation for completing the screening questionnaire.

The end of recruitment is at the end of the 2nd month post start of study. The last MRI scan is estimated to be at the end of the 5th month post start of study. The last letter of appreciation or final communication letter is estimated to be sent (at the latest) 6th month post start of study. The end of study is defined as 12 months after the start of study.

The Sponsor and CI have the right at any time to terminate the study for clinical or administrative reasons.

The CI shall notify the REC and the Sponsor in writing within 90 days of the study conclusion, or of the early termination of a study, using the NRES Declaration of the End of Trial Form available from the HRA website (http://www.hra.nhs.uk). The CI will ensure that any appropriate follow up is arranged for all participants.

The CI shall work with the Sponsor to prepare and submit to the REC and Sponsor a summary of the study within 12 months of the end of the study.

18. Publication and Dissemination

Authorship policy

Ownership of the data arising from this study resides with the CI and his/her respective employer. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, shall belong to the CI and his/her respective employer.

Publication

The clinical study report will be used for publication and presentation at scientific meetings. The CI will have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to stakeholders for dissemination (where appropriate and according to their discretion).

Publication plan

The intention is to publish in a specialist rheumatology journal. An initial abstract of the study with initial data on prevalence of CBP and IBP in IBD patients which may suggest a diagnosis of axSpA will be available approximately from the 10th to 11th month post start of study. The final abstract and journal submission will full data will follow approximately from 12th month post start of study depending on data analysis and administrative processes. This is only a tentative timeline outline which may be subjected to changes depending on the study's progress.

Recognition and Acknowledgement

All publications, communications, presentations, posters and broadcasts (or any other material) relating to the study will acknowledge the funders support.

Peer review

The project has been peer-reviewed in the following ways:

- The project has been reviewed by the NASS Medical Advisory Board and NASS Council of Management as part of the process in securing external funding competitively from the NASS (National Ankylosing Spondylitis Society) Research Grant in the 2017/2018 application.
- The project has been externally peer reviewed by Dr Raj Sengupta, Consultant Rheumatologist, Royal National Hospital for Rheumatic Diseases.
- The project has also been reviewed internally in the rheumatology department, gastroenterology department (Dr Mark Tremelling) and by Dr Karl Gaffney (Clinical/Educational supervisor) and by Professor Alexander MacGregor (Academic/Educational Supervisor).

Reporting

Reports will be produced for Sponsor, REC and R&D as agreed in contracts and approval letters.

19. References

1. Hamilton L, Barkham N, Bhalla A, Brittain R, Cook D, Jones G, et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology. 2017 Feb 1;56(2):313–6.

2. Keat A, Bennett AN, Gaffney K, Marzo-Ortega H, Sengupta R, Everiss T. Should axial spondyloarthritis without radiographic changes be treated with anti-TNF agents? Rheumatol Int. 2017 Mar;37(3):327–36.

3. Sieper J, Rudwaleit M, Khan MA, Braun J. Concepts and epidemiology of spondyloarthritis. Best Pract Res Clin Rheumatol. 2006 Jun;20(3):401–17.

4. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol. 2012 May;8(5):262–8.

5. Slobodin G, Eshed I. Non-Radiographic Axial Spondyloarthritis. Isr Med Assoc J IMAJ. 2015 Dec;17(12):770–6.

6. Lambert RGW, Bakker PAC, van der Heijde D, Weber U, Rudwaleit M, Hermann KG, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann Rheum Dis. 2016 Nov;75(11):1958–63.

7. Rudwaleit M, Jurik AG, Hermann K-GA, Landewé R, Heijde D van der, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis. 2009 Oct 1;68(10):1520–7.

8. Rudwaleit M, Landewé R, Heijde D van der, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial

spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009 Jun 1;68(6):770–6.

9. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009 Jun;68(6):777–83.

10. Zink A, Listing J, Klindworth C, Zeidler H. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. Ann Rheum Dis. 2001 Mar;60(3):199–206.

11. Seo MR, Baek HL, Yoon HH, Ryu HJ, Choi H-J, Baek HJ, et al. Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis. Clin Rheumatol. 2015 Aug;34(8):1397–405.

12. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009 Mar;60(3):717–27.

13. Sieper J, Heijde D van der, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013 Jun 1;72(6):815–22.

14. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatol Oxf Engl. 2015 Dec;54(12):2283–4.

15. Derakhshan MH, Pathak H, Cook D, Dickinson S, Siebert S, Gaffney K. Services for spondyloarthitis: a survey of patients and rheumatologists. Rheumatology [Internet]. [cited 2018 Feb 27]; Available from: https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/kex518/4907948

16. Back Pain Plus [Internet]. NASS. [cited 2017 Sep 24]. Available from: https://nass.co.uk/get-involved/campaigning/back-pain-plus/

17. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis. 2016 Nov 4;

18. de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis Res Ther. 2016 Sep 1;18:196.

19. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis. 2015 Jan;74(1):65–73.

20. Salvarani C, Fries W. Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease. World J Gastroenterol WJG. 2009 May 28;15(20):2449–55.

21. Stolwijk C, Essers I, van Tubergen A, Boonen A, Bazelier MT, De Bruin ML, et al. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. Ann Rheum Dis. 2015 Jul;74(7):1373–8.

22. El Maghraoui A. Extra-articular manifestations of ankylosing spondylitis: prevalence, characteristics and therapeutic implications. Eur J Intern Med. 2011 Dec;22(6):554–60.

23. Brown MA, Kenna T, Wordsworth BP. Genetics of ankylosing spondylitis--insights into pathogenesis. Nat Rev Rheumatol. 2016 Feb;12(2):81–91.

24. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol. 2006 Jun;20(3):451–71.

25. Braun J, Baraliakos X, Regel A, Kiltz U. Assessment of spinal pain. Best Pract Res Clin Rheumatol. 2014 Dec 1;28(6):875–87.

26. Sieper J. How to screen for axial spondyloarthritis in primary care? Curr Opin Rheumatol. 2012;24(4):359.

27. Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. Ann Rheum Dis. 2005 May;64(5):659–63.

28. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis. 2015 Nov;74(11):1990–5.

29. Leclerc-Jacob S, Lux G, Rat AC, Laurent V, Blum A, Chary-Valckenaere I, et al. The prevalence of inflammatory sacroiliitis assessed on magnetic resonance imaging of inflammatory bowel disease: a retrospective study performed on 186 patients. Aliment Pharmacol Ther. 2014 May;39(9):957–62.

30. Gotler J, Amitai MM, Lidar M, Aharoni D, Flusser G, Eshed I. Utilizing MR enterography for detection of sacroiliitis in patients with inflammatory bowel disease. J Magn Reson Imaging JMRI. 2015 Jul;42(1):121–7.

31. Hamilton L, Macgregor A, Newman D, Belkhiri A, Toms A, Gaffney K. Validation of a patient self-reported screening questionnaire for axial spondyloarthropathy in a UK Population. Spine. 2013 Mar 15;38(6):502–6.

32. Braun J, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. Ann Rheum Dis. 2010 Jul;69(7):1264–8.

33. Queiro R, Maiz O, Intxausti J, de Dios JR, Belzunegui J, González C, et al. Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. Clin Rheumatol. 2000;19(6):445–9.

34. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984 Apr;27(4):361–8.

35. Hermann K-GA, Baraliakos X, Heijde DM van der, Jurik A-G, Landewé R, Marzo-Ortega H, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. Ann Rheum Dis. 2012 Aug 1;71(8):1278–88.

36. Satsangi J, Silverberg MS, Vermeire S, Colombel J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749–53.

37. Braun J, Baraliakos X, Heldmann F, Kiltz U. Tumor necrosis factor alpha antagonists in the treatment of axial spondyloarthritis. Expert Opin Investig Drugs [Internet]. 2014 Apr 10 [cited 2018 Jan 16]; Available from: http://www.tandfonline.com/doi/abs/10.1517/13543784.2014.899351

38. Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). J Rheumatol. 2002 Mar 1;29(3):511–5.

39. Steer S, Jones H, Hibbert J, Kondeatis E, Vaughan R, Sanderson J, et al. Low back pain, sacroiliitis, and the relationship with HLA-B27 in Crohn's disease. J Rheumatol. 2003 Mar;30(3):518–22.

40. van Erp SJ, Brakenhoff LK, van Gaalen FA, van den Berg R, Fidder HH, Verspaget HW, et al. Classifying Back Pain and Peripheral Joint Complaints in Inflammatory Bowel Disease Patients: A Prospective Longitudinal Follow-up Study. J Crohns Colitis. 2016 Feb;10(2):166–75.

41. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990 Feb;33(2):160–72.

42. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 1994 Sep;21(9):1694–8.

43. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994 Dec;21(12):2286–91.

44. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994 Dec;21(12):2281–5.

45. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 1996 Jan;35(1):66–71.

46. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet Lond Engl. 1980 Mar 8;1(8167):514.

47. Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology. 2002 Feb 1;122(2):512–30.

48. Info HBI | Harvey-bradshaw index [Internet]. [cited 2018 Feb 28]. Available from: http://www.igibdscores.it/en/info-hbi.html

49. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987 Dec 24;317(26):1625–9.

50. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462–76.

51. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the Non-invasive Components of the Mayo Score to Assess Clinical Response in Ulcerative Colitis. Inflamm Bowel Dis. 2008 Dec;14(12):1660–6.

52. Info MAYO | Partial [Internet]. [cited 2018 Feb 28]. Available from: http://www.igibdscores.it/en/info-mayo-partial.html

53. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA. 1977 Jun 13;237(24):2613–4.

54. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum. 2006 Feb;54(2):569–78.

55. Sieper J, van der Heijde D, Landewé R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis. 2009 Jun;68(6):784–8.

56. Dougados M, Linden SVD, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group Preliminary Criteria for the Classification of Spondylarthropathy. Arthritis Rheum. 1991 Oct 10;34(10):1218–27.

57. Mandl P, Navarro-Compán V, Terslev L, Aegerter P, Heijde D van der, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis. 2015 Jul 1;74(7):1327–39.

58. Patient dose information: guidance - GOV.UK [Internet]. [cited 2017 Jul 30]. Available from: https://www.gov.uk/government/publications/medical-radiation-patient-doses/patient-dose-information-guidance

59. Patient Information Leaflets – Core [Internet]. [cited 2017 Aug 1]. Available from: http://corecharity.org.uk/resources-for-patients/patient-information-leaflets/

20. Appendices

A Invitation Letter
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University of East Anglia

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GASTROENTEROLOGY DEPARTMENT
Norfolk & Norwich University Hospital
Colney Lane
Norwich
NR4 7UY

Direct dial: 01603 288230
Direct fax: 01603 288368
Switchboard: 01603 286286

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label

Dear Sir/Madam,

Re: Recruitment To The N-ASPIRE Tool Study

We are undertaking a research project, with our colleagues in the rheumatology department, for patients who are being seen in the gastroenterology clinic with a diagnosis of inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis). They are particularly interested in people who have also suffered from back pain, either recently, or for a significant amount of time in the past. This could be a symptom of arthritis related to your inflammatory bowel disease.

Please find enclosed more information about the study. If you have any questions please contact the rheumatology department using the details in the PIS (Participant Information Sheet).

We would be grateful if you could complete the enclosed questionnaire and return it in the stamped addressed envelope.

Yours sincerely

Verified Electronically

Gastroenterology Department

Encs
- Participant Information Sheet
- Screening Questionnaire

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email: eleanor.sykes@nnuh.nhs.uk

LETTER OF APPRECIATION

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label

Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - axial SpA IBD referral Tool (N-ASPIRE Tool)]

Dear Sir/Madam,

Thank you for completing the questionnaire for the above study.

On review of the questionnaire, you did NOT fulfil the eligibility criteria OR decline to be contacted for the next phase of the study. As such, your participation will now end.

We value your time and effort in the participation of the study. Thank you.

If you have any questions please contact the Rheumatology Research Team.

Yours sincerely,

Dr Chong Seng Edwin Lim
Senior Research Fellow (Rheumatology)

Dr Karl Gaffney
Rheumatology Consultant

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PARTICIPANT INFORMATION SHEET

You are being invited to take part in a research study. Before you decide if you would like to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Feel free to contact us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. See Flow Chart for an overview on page 6.

Study Title

Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - Axial SPa Ibd REferral Tool (N-ASPIRE Tool)]

Study Title Explanation

A study to investigate the prevalence of axial spondyloarthritis (axSpA) in patients with known inflammatory bowel disease (IBD) such as Crohn's Disease (CD) and Ulcerative Colitis (UC). Using information from the study to develop a tool to facilitate referral of patients with suspected axSpA in patients with IBD to a rheumatology specialist.

What is the purpose of the study?

IBD can sometimes be associated with an arthritis called axSpA. The arthritis causes inflammation in the spine resulting in back pain, stiffness or reduced range of movement of the spine.

AxSpA is often diagnosed late because it is relatively uncommon cause of back pain and there are many other causes of back pain which may be investigated by your doctor first. It is, however, important to make this diagnosis as early as possible in order to receive the most effective treatment.

This study is to find out how many people with IBD also have axSpA. Further study of these participants' characteristics will help us to develop a tool to guide investigations in patients with IBD. This will reduce the time to diagnosis and enable earlier access to available treatments.

Why have I been chosen?

You have been under the care of the Gastroenterology Department at the Norfolk and Norwich University Hospital (NNUH) with IBD (CD or UC). Because you attended the gastroenterology department with a diagnosis of IBD, you have been invited to take part in this study.

We are interested in people who have had back pain at any point in the past, or who have ongoing back pain. However, even if you have never had back pain, we would be grateful if you could still return the attached questionnaire, indicating that you do not wish to take part, so that we don't send you a 2nd invitation letter.

Do I have to take part?

It is up to you whether you decide to take part or not. If you do decide to take part, then you should keep this information sheet and you will be asked to sign a consent form at a later stage.

If you would prefer not to take part in the study, we would still be grateful if you could return the enclosed questionnaire, ticking the "I would prefer not to take part in the study" box so that we do not send you a second invitation letter. A decision not to take part will not affect the standard of care you would otherwise receive within the NHS.

What will happen to me if I take part?

If you agree to take part, firstly you would need to complete the questionnaire enclosed with this letter and return it in the stamped envelope. See Flow Chart for an overview on page 6.

1. If the information provided on this questionnaire does NOT suggest that you could have axSpA, your participation will end at that point.
2. If the information provided on this questionnaire suggests that you could have axSpA or *you are a selected control patient**, you will be asked to attend a clinic appointment in the rheumatology department. At this appointment you will be asked some questions and be examined by a rheumatology specialist doctor.

*The voluntary participation from a small proportion of patients who may not show typical features of the axSpA (e.g. chronic back pain) will be requested if a completed questionnaire have been returned and have agreed to be contacted for the clinical assessment phase of the study. These are the control patients. You will be contacted individually by the research team with more details. An X-ray of the pelvis will NOT be performed in this group.

At the appointment with the rheumatology doctor, you will undergo a medical interview, physical examination and rheumatological measurements. You will then have some blood taken (which will be discarded after analysis) and be booked for a radiograph (X-ray) of your pelvis. You will attend a Magnetic Resonance Imaging (MRI) scan in the radiology department at a second visit after the initial rheumatology clinic visit. The scan will last around 30 minutes and will look at your mid-to-lower back and pelvis,

whilst your head will stay out of the scanner. You will find a NNUH patient information leaflet on X-ray and MRI scanning enclosed.

Your travel expenses for attending the study visits will be reimbursed (maximum of £10 pounds per participant per visit).

We will inform you and your General Practitioner (GP) of the diagnosis including any unexpected results. Your participation in this study will end at that point. Any further care you may require will be arranged through your GP.

What are the possible benefits of taking part?

You will have an opportunity to find an explanation for your back pain. If you are found to have inflammation in your spine or other potentially treatable causes of back pain, we will recommend that your GP refer you to the main rheumatology clinic and you may be given treatment to help manage your symptoms.

What are the possible disadvantage and risks of taking part?

We may be able to diagnose you with having axSpA which may have implications for your day-to-day life (as being diagnosed with any chronic disease would) but we hope that the opportunity to start treatment earlier would outweigh any distress of this findings.

There are some risks and discomfort associated with the study procedures outlined below:

- Blood collection: For most people, needle puncture for blood withdrawal do not cause any problems. However, sometimes they may cause bleeding, bruising, discomfort, infections, and/or pain where the skin is punctured. You may also feel dizzy.
- X-rays: You will have 1 (one) X-ray of your pelvis during the study. You will be exposed to a small amount of radiation during the test. The radiation that you receive from this test is about the same as what you would be exposed to in 16 weeks normally from all sources (natural and man-made). The x-ray may be slightly uncomfortable, as you may have to lie on your back. You may opt out of this investigation if the risk is deemed unacceptable to you. See attached NNUH Plain X-ray Patient Information leaflet for more information.
- MRI: The risks associated with having an MRI of the spine and pelvis are very minimal. However, if you are claustrophobic (have a fear of closed spaces) or have had any metal placed in your body (for example, during a surgery), **you should let us know if we contact you to arrange a clinic appointment.** See attached NNUH MRI Patient Information leaflet for more information.

As with any test, we would like to make you aware that there is a possibility that the results of the above investigations may identify another cause for your symptoms which may be unrelated to the study. This information will be forwarded to you and your general practitioner who will decide on your further care.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time without giving a reason if you wish and this will not affect your standard of care. If you do withdraw from the study, we will destroy all of your identifiable personal data, but unless you specifically ask otherwise, we will retain and use any anonymised research data collected as part of the study, up to that point.

Will my taking part in this study be kept confidential?

Yes. All study materials will be kept confidential and we will use a unique study number to identify you. Your name and contact details will be stored separately from all other study materials and all data storage (both paper and electronic) will be kept secure at all times – only study personnel who need to will have access to your data. Electronic data will be kept securely on Trust computers with password-protected access and we will comply with all Data Protection legislation.

If you consent to take part in the research, any of your medical records may be inspected by the institution/company funding or sponsoring the research for purposes of analysing the results. They may also be looked at by people from the institution/company, regulatory authorities and hospital trust to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

We would routinely inform your GP that you have agreed to take part in the study and we would also inform your GP of the results of the study. In Phase 1 (Questionnaire) of the study you can choose to opt out of this process.

Your personal data and research data will be keep for a minimum of 5 years after the end of the study according to the Trust's policy.

What will happen to the results of the study?

You will be contacted by letter with your individual results and a copy of this letter will also be sent to your GP.

The final study report will be published in a medical journal or at a medical conference. The final report will NOT include any personal details, and NO individual participants will be identified.

We will ask your permission for your anonymised data (this data that will NOT include any personal details, and NO individual participants will be identified) to be shared with the wider research community for ethically approved future studies.

Who is organising and funding the research?

The research is being organised by the Rheumatology Department of Norfolk and Norwich University Hospital NHS Foundation Trust in collaboration with the University of East Anglia (UEA). The funding for the study has been partly provided by the charity NASS (National Ankylosing Spondylitis Society) and the NNUH Rheumatology Department.

Who has reviewed the study?

All Research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the East of England – Cambridgeshire and Hertfordshire Research Ethics Committee.

What if something goes wrong?

Independent advice is available from the Patient Advocacy and Liaison Service (PALS) and the Independent Complaints Advisory Service (ICAS).

PALS: PALS Office
Level 2 West Outpatient
Norfolk and Norwich University Hospital
01603 289045

ICAS: 01273 229 002

Contacts for further information

If you require any additional information, please do not hesitate to contact either Dr Edwin Lim or Dr Karl Gaffney.

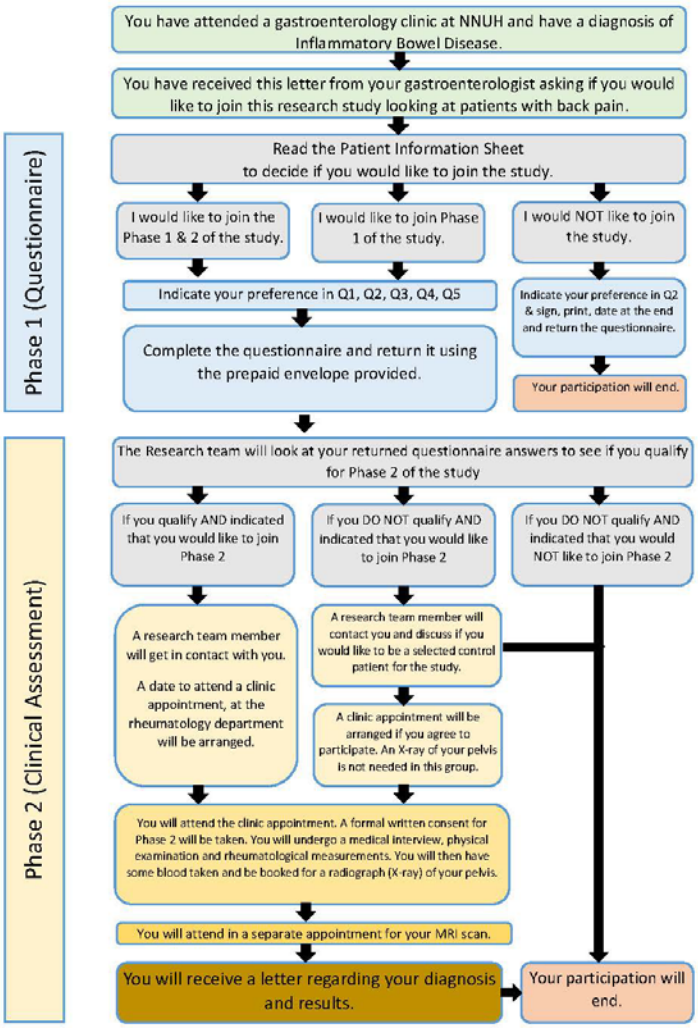
Rheumatology Department
Norfolk and Norwich University Hospital NHS Foundation Trust,
Colney Lane,
Norwich NR4 7UY
01603 647835 or 01603 287119

What happens next?

If you would like to take part in the study, please complete the enclosed questionnaires and return it in the envelope provided.

Thank you for your consideration in taking part in this study

Flow Chart – Your Journey



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email: eleanor.sykes@nnuh.nhs.uk

PARTICIPANT CONSENT FORM

Study Title: Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - axial SpA IBD referral Tool (N-ASPIRE Tool)]

Investigators: Dr Chong Seng Edwin Lim; Dr Karl Gaffney

Patient Full Name:	
Personal Identification Number (PIN)	

	Please read the following statements and put your initials in the box to show that you have read and understood them and that you agree with them.	**Please initial each box**
1	I confirm that I have read and understand the information sheet Version ____ dated _____ for the above study. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.	
2	I understand that my involvement is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	
3	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals, from the research team, from the Sponsor or authorised by the Sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4	I agree to be contacted by the study team for ethically approved future studies that they may be undertaking. I understand that identifiable contact information will be kept after the end of this study and this information will be held in accordance with data protection legislation.	
5	I agree for my data (paper or electronic) to be stored and retained according to the data standard operation procedures of the sponsor institution.	
6	I agree for anonymised data to be shared with the wider research community for ethically approved future studies.	

ONE copy for patient, ONE copy for medical notes, ORIGINAL to be file in Study File

Opting out of pelvic radiography (X-ray). Choose one of the two options below. (NOT needed for SNAC Group)		
7a	After considering the risk and benefit, I **AGREE** to a pelvic radiograph.	
7b	After considering the risk and benefit, I prefer **NOT** to have a pelvic radiograph	
Involvement of your General Practioner (GP).		
8	I agree to my GP being informed of my participation in the study and the results of any investigations including unexpected findings or an adverse event.	
Additional statement for SNAC Group only.		
9	I understand I am in the Screen Negative Assessment Control (SNAC) Group and have understood the counselling given. I understand that screening can lead to positive findings in the assessment but may not have any clinical significance.	
Pregnancy Status for female subjects only.		
10	I confirm that there is **NO** chance of pregnancy.	

To be completed by the participant **I freely agree to take part in the above study**		
Your name	Date (Day/Month/Year)	Signature

To be filled in by the person obtaining consent (investigator)		
Is participant in SNAC Group (circle response):	Yes / No	
I confirm that I have explained the nature, purposes and possible risk and benefit the research study to the person whose name is printed above. They agreed to take part by signing and dating above.		
Your name	Date (Day/Month/Year)	Signature

ONE copy for patient, ONE copy for medical notes, ORIGINAL to be file in Study File

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Eleanor Sykes

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Norwich
NR4 7UY

Direct dial: 01603 287621
Direct fax: 01603 287004
Switchboard: 01603 286286

email: eleanor.sykes@nnuh.nhs.uk

GP Information Sheet

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label

Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - axial SpA IBD referral Tool (N-ASPIRE Tool)]

The above named patient is known to the gastroenterology team at the Norfolk and Norwich University Hospital with a diagnosis of Inflammatory Bowel Disease (IBD).

As IBD is often associated with axial spondyloarthritis (axSpA), this study has been proposed to investigate the hidden prevalence of axSpA in this group of patients.

This man/women has been contacted and has agreed to take part in the study.

Last paragraph will be added depending on scenario (Delete as necessary):

- **We will assess the patient in the rheumatology department and inform you of the results afterwards.** *(Screen positive and agree for contact in Phase 2 or SNAC Group)*
- **The patient has completed a screening questionnaire but has not agreed to join the clinical phase of the study. Their participation has ended.** *(Screen positive but decline for participation in Phase 2)*
- **The patient has completed a screening questionnaire but is not eligible for the clinical phase of the study. Their participation has ended.** *(Screen negative regardless of interest to participation in Phase 2 or screen positive but has exclusion/pregnancy status uncertain)*

Yours sincerely,

Dr Chong Seng Edwin Lim
Senior Research Fellow (Rheumatology)

Dr Karl Gaffney
Rheumatology Consultant

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University of East Anglia

PIN _____

SCREENING QUESTIONNAIRE

Please kindly fill in ALL the BLANKS and mark the ☐ with a CROSS ☒ as you go through the questionnaire sequentially.

Subject's details and consent

Q1 About yourself (all information will be strictly confidential)

Full Name:			
Date of Birth:		Age:	
Address:			
Main contact number:			
Gender:	Male ☐	Female ☐	Prefer not to say ☐

Q2 I have read the attached Participant Information Sheet and I would prefer NOT to take part in the study. ☐

If you have indicated that you prefer NOT to take part in the study, there is NO need to complete the rest of the questionnaire. Please sign and date the form at the end. Kindly return it to us in the prepaid envelope. Thank you.

Q3 I have read the attached Participant Information Sheet:- (**Choose ONE option below**)

- *I am happy to complete this questionnaire **AND** to be contacted for an appointment to attend the rheumatology department for clinical assessment (Phase 2 of study).* ☐
- *I am happy to complete this questionnaire **BUT** I prefer **NOT** to take part in the clinical assessment (Phase 2 of study).* ☐

Q4 Data Access and Storage:- (**Select ALL that apply**)

- *I give permission for the researchers to access and use all my relevant medical information for the purpose of this study.* ☐
- *I understand that my medical notes and information collected during the study may be looked at by responsible individuals (Research Team, Sponsors, Regulatory Authorities, NHS Trust) where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.* ☐
- *I agree to be contacted by the study team for future studies. I understand that identifiable contact information will be kept after the end of this study and this information will be held in accordance with data protection legislation.* ☐
- *I agree for my information/data (paper or electronic) to be stored and retained according to the sponsor's standard operating procedures.* ☐
- *I agree for my data to be shared with the wider research community for future studies if I cannot be identified in the data.* ☐

Q5 Involvement of your General Practioner (GP):- (**Choose ONE option below**)

- *I AGREE to my GP being informed of my participation in the study.* ☐
- *I would prefer that my GP was NOT informed of my participation in the study.* ☐

Subject's previous diagnosis

Q6 I already have a diagnosis of:

Anklyosing Spondylitis ☐
Axial sponlyloarthritis/sponlyloarthropathy ☐
If yes, please provide further details in the box below (e.g. who made the diagnosis, whether you attend hospital outpatients appointments, when it was diagnosed).

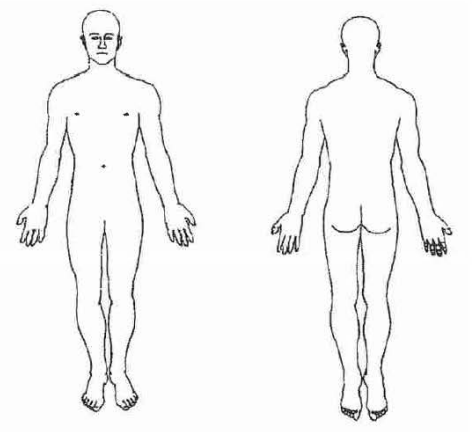
We will review your medical records and if we are able to verify this then you do not need to continue with the Phase 2 of the study. Thank you.

Main questionnaire

Q7 Have you had back pain or stiffness lasting for at least 3 months?

YES ☐
NO ☐

If yes, please mark the site of pain on the diagram



Q8 How old were you when the pain started?

- Less than 18 years old ☐
- 18 – 25 years old ☐
- 26 – 33 years old ☐
- 34 – 40 years old ☐
- 41 – 44 years old ☐
- more than 44 years old ☐

Q9 Did the pain or stiffness start:

- Gradually ☐
- Suddenly (e.g. after falling / lifting / twisting) ☐

Q10 Have you had pain or numbness spreading down your legs?

- YES ☐
- NO ☐

Q11 Have you had buttock pain which moves from side to side?

- YES ☐
- NO ☐

Q12 Are you woken up by back pain or stiffness?

- First half of the night ☐
- Second half of the night ☐
- Throughout the night ☐
- Not woken up ☐

Q13 What happens to your pain/stiffness as the day goes on?

- Gets better ☐
- Gets worse ☐
- No change ☐

Q14 If it gets better, how long does this take:

- Within 15 mins ☐
- Within 30 mins ☐
- Within 60 mins ☐
- Within 2 hours ☐
- More than 2 hours ☐

Q15 What effect does exercise have on your back pain and stiffness?

- Increases pain/stiffness ☐
- Decrease pain/stiffness ☐
- No effect on pain/stiffness ☐

Q16 What effect dose resting have on your back pain or stiffness?

- Increases pain/stiffness ☐
- Decrease pain/stiffness ☐
- No effect on pain/stiffness ☐

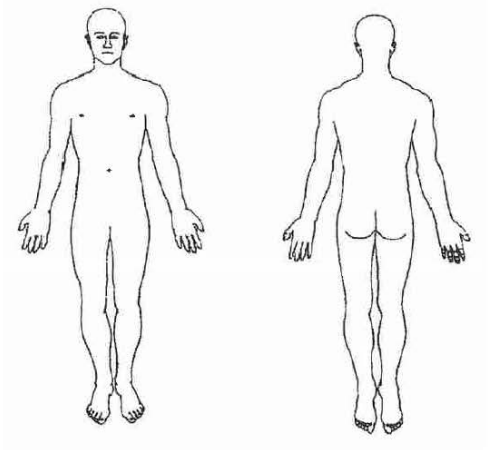
Q17 What effect do anti-inflammatory drugs (e.g. ibuprofen, diclofenac, naproxen) have on your back pain?

- Increases pain/stiffness ☐
- Decrease pain/stiffness ☐
- No effect on pain/stiffness ☐
- I havent taken anti-inflammatories ☐

Q18 Have you had pain in any other places e.g. joints, heels?

- YES ☐
- NO ☐

If YES, please mark on diagram (below):



Q19 Do any close relative (parents, children, brothers or sisters) have:

- Anklyosing Spondylitis or Axial sponlyloarthritis/sponlyloarthropathy ☐
- Anterior Uveitis / Iritis ☐
- Psoriasis ☐
- Inflammatory Bowel Disease ☐
- Reactive Arthritis ☐

Q20 Have you ever been diagnosed with any of the following conditions

- Reactive Arthritis ☐
- Achilles Tendinitis (Enthesopathy) or Plantar fasciitis ☐
- Dactylitis ☐
- Psorasis ☐
- Anterior Uveitis / Iritis ☐

Brief Inflammatory Bowel Disease (IBD) questionnaire

Q21 Please indicate the type of IBD you are diagnoses with?

- Crohn's Disease ☐
- Ulcerative Colitis ☐

Q22 What was the age when your IBD symptoms started and diagnosed by your gastroenterologist?

- Age symtpoms started (give an estimate rounded number): ☐
- Age diagnosis made by gastroenterologist (give an estimate rounded number): ☐

Q23 How long have you been had you diagnosis of IBD?

- Duration of your IBD diagnosis: ☐
  (Give an estimate rounded number in months e.g. 1 yr + 1 mth = 13 months)

Q24 Please indicate the types of treatment you are <u>currently</u> on for the treatment or manaintence of your IBD (select as many as needed)?

Rectal topical steriods e.g. hydrocortisone, etc	☐
Rectal aminosalicylate (5-ASA) medications e.g. mesalazine, etc	☐
Oral steriods e.g. budesonide, prednisolone, beclometasone, etc	☐
Oral aminosalicylate (5-ASA) medications e.g. mesalazine, olsalazine, sulfasalazine, etc	☐
Immunomodulator therapy e.g. azathioprine, mercaptopurine, methotraxate, etc	☐
Biological therapy e.g. infliximab, adalimumab, vedolizumab, ustekinumab, etc	☐
None. I am not on any treatment.	☐
Others. Not stated in the groups above. Please describe in the box below:	☐

Q25 Please indicate if you had the following due to your Inflammatory Bowel Disease?

Previous surgery for your Inflammatory Bowel Disease?	☐
Hospitalisation due to your Inflammatory Bowel Disease?	☐

Q26 How would you describe your current Inflammatory Bowel Disease activity?

Remission (NOT active)	☐
Mild	☐
Moderate	☐
Severe	☐
Unsure	☐

Q27 Do you know what your gastroenterologist think about your current IBD activity?

Remission (NOT active)	☐
Mild	☐
Moderate	☐
Severe	☐
Unsure	☐

Thank you.
You have come to the end of the questionnaire.
Please return it in the prepaid envelope.

Signature:	
Print Name:	
Today's Date:	

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

University of East Anglia

CASE REPORT FORM

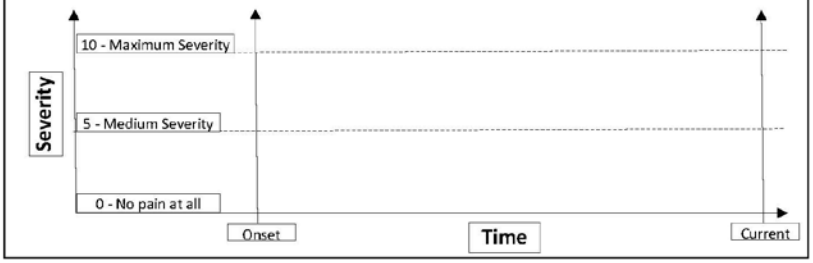
PIN _____ DATE SEEN: _____

Section 1: Structured History

ITEM 1	Demographics & Habits
Gender:	
Age:	
Alcohol:	current intake in units/week
Smoking:	never/ex/current smoker & pack years

ITEM 2	Description of back pain
Age of 1st onset of back pain	
Site of back pain?	cervical / thoracic / lumbar / mixed / not around spine
Radiation to legs?	yes / no
Alternating buttock pain?	yes / no
Gradually onset?	yes / no
Duration of back pain ≥ 3mth	yes / no
When is the back pain/stiffness worse?	morning / afternoon / evening / whole day
Are you woken by back pain/stiffness?	1st ½ of night / 2nd ½ of night / whole night / Not woken up
What happens to your pain/stiffness as the day goes on?	better / worse / no change
If it gets better, how long does this take?	15 / 30 / 60 / 120 / >120min
What effect does exercise have on your back pain and stiffness?	increase / decrease / none
What effect dose resting have on your back pain or stiffness?	increase / decrease / none
What effect do anti-inflammatory drugs have on your back pain?	increase / decrease / none / not taken anti-inflammatories
Do you think there is IBP (inflammatory back pain)	yes / no
Description & Comments (free text):	

ITEM 3	Back Pain Pattern Graph



PIN _____

ITEM 4	Details of axSpA associated conditions
Previous/Current diagnosis of arthritis, enthesitis or dactylitis	yes / no ; A / E / D
Previous/Current diagnosis of other muculoskeletal problems?	yes / no
Muculoskeletal problem details: (Diagnosis, number, location, treatment)	
Previous/Current diagnosis of anterior uveitis?	yes / no
Previous/Current diagnosis of eye problems?	yes / no
Eye problem details: (Diagnosis, number of episodes, treatment received within past year)	
Previous/Current diagnosis of psoriasis?	yes / no
Previous/Current diagnosis of skin problems?	yes / no
Skin problem details: (Diagnosis, current status, treatment received within past year)	
Previous/Current diagnosis of IBD?	yes / no
Type (CD or UC)?	CD / UC
Age of symptom onset (estimation in years)?	
Age of diagnosis (estimation in years)?	
Duration of disease since diagnosis (estimation in months)?	
Did you receive treatment for your IBD previously?	yes / no
Are you current on treatment for your IBD?	yes / no
Are you currently on steriods?	yes / no
Are you on biological therapy?	yes / no
Previous operations for IBD?	yes / no
Previous hospitalisation for IBD?	yes / no
Do you know your gastroenteriologist's impression of your current IBD activity?	remission / mild / moderate / severe / unsure
How do you rate your current IBD activity?	remission / mild / moderate / severe
IBD and Treatment details: (Previous & Current Treatment details; either from patient or medical records or re-verified with gastroenteriologist. [1] basis of IBD diagnosis [2] extend or classification of disease [3] current disease activity) Recorded last current IBD activity by Gastroenterologist (e.g HBI/partial Mayo index/Others if present) - Not active (remission); Active (mild/moderate/severe); Unclear; Not recorded	

ITEM 5	Other past medical history / Co-morbidity

PIN _____

ITEM 6	Allergies and current medications		
Do you use NSAIDS for your musculoskeletal symptoms?			yes / no
Type	Dose	Frequency	Effect on pain/stiffness
			increase / decrease / none
Others medications & analgesia:			

ITEM 7	Family History and Social History	
Do any close relative (parents, children, brothers or sisters) have Anklyosing Spondylitis or Axial sponlyloarthritis/sponlyloarthropathy; Psoriasis; Anterior Uveitis; Reactive Arthritis; Inflammatory Bowel Disease?		yes / no
Details / Any other significant family history?		
Occupation / Others?		

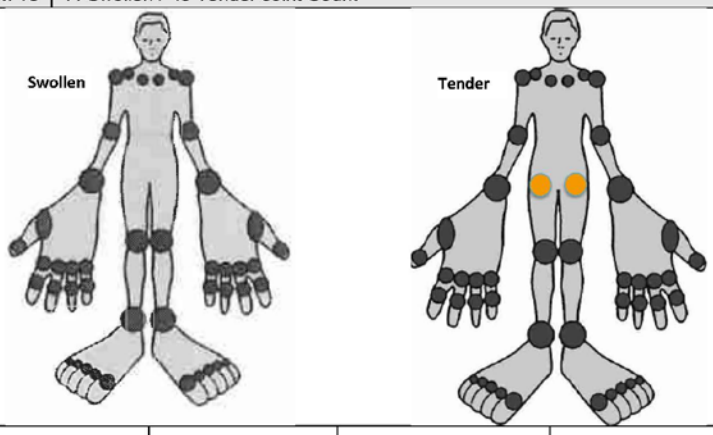
ITEM 8	Any other relevant symptoms/history/notes

Section 2: Structured Examination

ITEM 9	General Examination
• Weight, Height, BMI • Skin = check for psoriasis espically elbows, nails, umbilicus, natal clef or flexure of breast • GALS screen • Eyes, CVS, Resp, Abdo, Neuro	

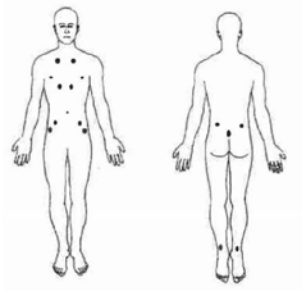
PIN _____

ITEM 10	44 Swollen / 46 Tender Joint Count



Swollen Joints	/44	Tender Joints	/46

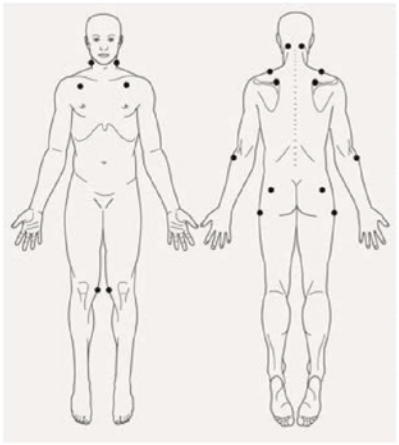
ITEM 11	Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)



Site	R	L
1st Costochondral		
7th Costochondral		
Anterior superior iliac spine		
Iliac Crest		
Posterior superiour iliac spine		
L5 spinous process		
Proximal achilles tendon insertion		
MASES	/13	

ITEM 12	Dactylitis Count
Number of digits with clinical dactylitis	/20
Details: (name the digit, record tenderness yes/no)	

PIN _____

ITEM 13	Tender points examination (ACR 1990 Fibromyalgia Classfication Criteria)		
	Site	R	L
	Suboccipital		
	Lower cervical (laterall by the C5-C6 tranverse processes)		
	At the midpoint of the upper Trapezius border		
	Suprapinatus by its orgin medially in the supraspinatus fossa		
	Intercoastal space above the 2nd rib and just lateral to the costochrondral junction		
	2cm distal to the lateral epicodyle		
	In the centre of the upper lateral quadrant of the gluteal region		
	Greater tronchanter		
	Medially on the medial femur condyle, just proximal to the joint line		
	Total number of tender point that are positive	/18	
	Evidence of widespread pain (4 quardants of the body) for > 3 months	yes / no	
	Clinical impression of fibromyalgia	yes / no	

PIN _____

Section 3: Rheumatological Outcome Measures

ITEM 14	BASMI & Other Measurements														
Category	Measurements														
Chest expansion (x2 difference reading, level of the 4th intercoastal level, higher of the two reading recorded)	1st		2nd		Best										
Occiput-to-wall distance (x2 readings, lower of the two readings recorded)	1st		2nd		Best										
Category	BASMI Measurements														Score
Tragus-to-wall distance (x2 readings, lower of the two readings recorded, REPEAT, mean of the lower reading of each side recorded)	R1		R2		Best		L1		L2		Best		Mean		
Lateral spinal flexion (x2 readings, higher of the two readings recorded, REPEAT, mean of the higher reading of each side recorded)	R1		R2		Best		L1		L2		Best		Mean		
Lumbar flexion (Modified Schobers) (x2 difference reading, level of the lumbosacral junction, higher of the two reading recorded	1st		2nd		Best										
Cervical rotation (x2 readings, higher of the two readings recorded, REPEAT, mean of the higher reading of each side recorded)	R1		R2		Best		L1		L2		Best		Mean		
Intermalleolar distance (x2 readings, higher of the two readings recorded)	1st		2nd		Best										
													BASMI =		
ITEM 15	Patient report outcome measures (PROMS)														
BASDAI		Notes:													
BASFI															
BASG															

PIN _____

Section 4: Gastroenterology Disease Activity (Depends on Type of IBD)

ITEM 16	Disease Activity for Crohn's Disease – HBI (Harvey-Bradshaw Index)	
No.	Details	Score
A	General wellbeing (0=very well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)	
B	Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)	
C	Number of liquid stools per day	
D	Abdominal mass (0=none, 1=dubious, 2=definite, 3=definite and tender	
E	Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item).	
	TOTAL Score =	
	Score Definition =	

Calculation:
- Calculation formula: sum of the scores of all 5 parameters.
- A score below 5 is generally considered as clinical remission. A reduction of 3 points is considered as relevant to define clinical response.

Scoring definition:
- Remission < 5; Mild Disease 5-7; Moderate Disease 8-16; Severe Disease >16

Source:
- Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet Lond Engl. 1980 Mar 8;1(8167):514.
- Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002; 122: 512-530.
- Info HBI | Harvey-bradshaw index [Internet]. [cited 2018 Feb 28]. Available from: http://www.igibdscores.it/en/info-hbi.html

ITEM 17	Disease Activity for Ulcerative Disease – PMS (Partial Mayo Score)	
No.	Details	Score
1	Stool Frequency (per day) [0=normal number of stool, 1=1-2 more than normal, 2=3-4 more than normal, 3=≥5 more than normal]	
2	Rectal Bleeding (indicate the most severe bleeding of the day) [0=none, 1=streaks of blood with stool in less than half of the cases, 2=obvious blood with stools in most cases, 3=blood alone passes]	
3	Physician's global assessment [0=normal, 1=mild disease, 2=moderate disease, 3=severe disease]	
	TOTAL Score =	
	Score Definition =	

Calculation:
- Calculation formula: sum of the scores the three parameters.

Scoring definition:
- Remission < 2; Mild Disease 2-4; Moderate Disease 5-7; Severe Disease >7

Source:
- Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Eng J Med 1987; 317 (26): 1625-1629.
- Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005; 353 (23): 2462-2476.
- Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008; 14 (12): 1660-1666.
- Info MAYO | Partial [Internet]. [cited 2018 Feb 28]. Available from: http://www.igibdscores.it/en/info-mayo-partial.html

PIN _____

Section 5: Investigation Results

ITEM 18	Laboratory Results	
HLA B27	positive / negative	
CRP	mg/L	
ESR	mm/hr	

ITEM 19	Imaging Results
X-ray of AP pelvis	MRI of Sacroiliac Joints & Spine
Radiology MDT discussion notes (if imaging have been discussed)	

Section 6: Diagnosis

ITEM 20	PVD of axSpA OR Alternative diagnosis

Section 7: Classification

ITEM 21	IBP Classification		ITEM 22	axSpA Classification	
Meet Calin IBP Criteria		yes / no	Meets mNYC AS criteria		yes / no
Meet Berlin IBP Criteria		yes / no	Meets ESSG axSpA criteria		yes / no
Meet ASAS IBP Criteria		yes / no	Meets ASAS axSpA criteria		yes / no
Notes:					

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University of East Anglia

RHEUMATOLOGIST DIAGNOSIS SHEET

Rheumatologist initials: _____

PIN	Dx of axSpA before reviewing Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible	Dx of axSpA after reviewing Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible

Rheumatologist initials: ________________

PIN	Dx of axSpA w/o Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible	Dx of axSpA with Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible

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Norfolk and Norwich University Hospitals NHS
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DEPARTMENT OF RADIOLOGY

Plain X-ray Information

The leaflet tells you about having an X-ray. It explains what is involved and what the possible risks are. It is not meant to replace informed discussion between you and your Doctor, but can act as a starting point for such discussions. If you have any questions about the procedure please ask the Doctor or healthcare professional who has referred you for the test, or the department which is going to perform it.

The Radiology department
Radiologists are doctors specially trained to interpret the images and carry out more complex examinations. Radiographers are highly trained professionals and carry out X-rays and other imaging procedures. A Radiographer will perform your X-ray, with a Radiologist or Reporting Radiographer interpreting the image afterwards.

What is an X-ray?
An X-ray is a picture of the internal structures of the body produced by exposure to a controlled source of X-rays. Images are recorded in digital form, shown on a computer screen.

Are there any risks?
There are risks involved with X-rays, but a plain X-ray uses a small amount of radiation, usually equivalent to that which we all receive from the atmosphere over a period of days to years (depending upon the area being X-rayed).

Female patients who are or might be pregnant ***must*** inform the Radiographer. Depending on which body part is to be X-rayed, the Radiographer will discuss with you whether it is appropriate for you to have the X-ray. They may ask that you have a pregnancy test.

Are you required to make any special preparations?
No. However, please notify the Radiology department if you have had a similar X-ray recently or if you are a woman who is or might be pregnant.

Can you bring a relative/friend?
Yes, but for reasons of safety, they will not be able to accompany you into the examination room, except in very special circumstances or in the case of young children.

When you arrive
You should go to the reception desk in the on Level 2, East Block, after which you will be shown where to wait until collected by a Radiographer or other member of staff.

The procedure for your examination will be explained to you. For certain X-ray examinations, you will be asked to undress and/or remove jewellery for the procedure. You will be shown to a private cubicle where you will be asked to put on the gown provided. You will be asked to place your clothes and personal items in a basket, which you will keep with you. Depending on what part of your body is being X-rayed, you may also be asked to remove your glasses, dentures or piercings as well.

Author: EKY January 2013 1
Reviewed: EKY November 2016 version 3 Review date: EKY/JHR November 2018
Adapted from the Royal College Of Radiologists leaflet "Information for patients having an X-ray" (2010)

What happens during the X-ray?
The Radiographer will first ask you your date of birth and address to confirm your identity. They will give you instructions throughout the examination and position you in order to take a number of images. Although the Radiographer will go behind a screen, you will be seen and heard at all times. The X-ray should not be uncomfortable or painful.

How long will it take?
This will vary, depending upon the body part being examined and the complexity of the images requested, in order to take diagnostic images. Waiting times will also vary, depending upon whether you have a booked appointment or not, and the number/type of clinics in the hospital.

Are there any side-effects?
None at all.

When will you get the results?
The images will be examined after your visit by a Radiologist or reporting Radiographer. A written report on the findings will be sent to your referring Doctor or healthcare professional Please discuss the findings of your X-ray with your Doctor. If you have been sent from clinic as a walk in patient, your hospital doctor will discuss the findings of the images with you directly.

Finally
Some of your questions should have been answered by this leaflet, but remember that this is only a starting point for discussion about your treatment with the Doctors/healthcare professionals looking after you. Make sure you are satisfied that you have received enough information about the procedure.

Access to Radiology

How to find us:	East Outpatients entrance and follow the signs to Level 2 or 3 Radiology (more information will be on your appointment letter). For appointments at Cromer Hospital, follow signs to Radiology. You can find more information at: www.nnuh.nhs.uk
Hospital transport:	To enquire about hospital transport telephone 0333 240 4100
Contact details:	**Telephone:** 01603 286048 (Outpatients) / 01603 286544 (GP patients) **Email:** radiology@nnuh.nhs.uk **Website:** www.nnuh.nhs.uk

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DEPARTMENT OF RADIOLOGY

Magnetic Resonance Imaging (MRI)

What is an MRI scan?
MRI (Magnetic Resonance Imaging) creates high resolution images of the body on a computer using a powerful magnet and radio frequency waves. MRI is a very safe way of producing images that can diagnose medical conditions. Unlike CT (Computed Tomography) it does not use X-rays and has not been shown to have any harmful side effects.

What does it involve?
The MRI scanner is a long open ended tube, surrounded by a large magnet present in the circular area. You will be asked to lie on a scanning table, which will be moved slowly so the part of your body being scanned is in the centre of the scanner. It is important that you remain as still as possible, so that we can get the best images. You will be positioned either head first or feet first depending on the area to be scanned. You will be given ear protection because the scanner makes a loud drumming noise. During the scan, the radiographer will be able to see you from the control room, and hear you via a two-way intercom.
Sometimes an injection will be required to give clearer pictures of certain tissues or organs being examined, but this will be discussed with you if it is necessary.

Will I feel anything?
MRI is entirely painless. You should not feel any discomfort during the scan and experience no after effects.

How long will the scan take?
The length of the scan depends upon the part of the body being imaged and the information your doctor needs. The scanning time can range from 10 minutes being the shortest scan time to 2 hours in length. Although we try our best to keep to appointment times, there can sometimes be unexpected delays.

How do I prepare for my scan?
Most MRI scans need no special preparation. You should continue with any medication. Instructions will be detailed in your appointment letter if necessary. You may eat and drink normally after the procedure.

What happens when I arrive?
You may be asked to change into a gown. Storage may be provided for valuables, but it is advisable to leave them at home. You will not be permitted to take them into the scan room with you.
Prior to your appointment, you will be sent an MRI Safety Questionnaire to complete. This will be checked by the radiographer before your scan to ensure you are safe to have the procedure.

Safety Precautions:
It may not be possible for certain patients to have this examination due to the strong magnetic field produced by the MRI scanner. This can be dependent on implants within your body or operations you have had.
Please contact the MRI department if you have any doubts about your suitability for an MRI scan.
You will need to remove the following before your appointment:

- Jewellery
- Body piercings

Can pregnant women have MR scans?
There have been no reported effects from MRI to the unborn child. We advise against scanning in the first trimester as a precaution. In certain critical cases, it may be necessary to be scanned during pregnancy when a more invasive diagnostic test would otherwise have to be performed.

Results of the scan:
The radiographers are qualified MRI professionals who specialise in obtaining high quality images, but are not trained to diagnose problems from the scans. A radiologist is a doctor training in reading MRI scans, they will examine the images after your test and complete a report of your scan.
The results of your MRI scan will be sent to the referring doctor who will arrange a follow up appointment.

If you have any questions regarding the scan please contact the MRI appointments office:

Telephone: **01603 286107 (Norfolk & Norwich)**
01603 646163 (Cromer)
E-mail: radiology@nnuh.nhs.uk
Website: www.nnuh.nhs.uk

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www.corecharity.org.uk

INFORMATION ABOUT

CROHN'S DISEASE

WHAT WHY WILL HOW OR IF WHEN

CROHN'S DISEASE

Crohn's Disease is an illness in which inflammation develops in parts of the gut leading to symptoms such as diarrhoea, abdominal pain and tiredness.

The inflammation can be mild in many cases but can sometimes be severe requiring strong medication or an operation to remove an affected part of the intestine. Crohn's Disease is one of the two conditions known as Inflammatory Bowel Diseases (IBD); with the other being ulcerative colitis. The symptoms and effects are similar to those of gastroenteritis (food poisoning) but differ in that they are not due to an infection and persist for a long time or until treated.

WHO GETS CROHN'S DISEASE?

The disease affects mainly young adults but can affect teenagers or younger children and can sometimes start later in life. Men and women are affected equally. Crohn's Disease affects about 1 in 1000 people (most people know one person affected by the condition). Crohn's Disease and ulcerative colitis can run in families – about one-fifth of people with the condition will have another family member affected[1].

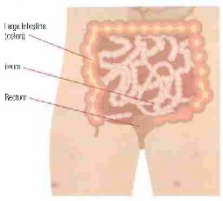
WHAT CAUSES IT?

It is thought that Crohn's Disease develops as a result of the immune system in the intestine reacting abnormally to bacteria at the surface of the gut. This abnormal immune reaction is likely to be inherited with a number of genes that may contribute to causing Crohn's Disease having now been identified, which are mostly involved in how we handle bacteria in the gut[2].

It is still not known if one, a few or many types of bacteria are involved. Other factors affect the chances of getting Crohn's Disease, with smoking being the most important risk factor[3]. Many patients ask whether there is a dietary cause but there is no firm evidence of this[4].

WHICH PART OF THE BODY DOES CROHN'S DISEASE AFFECT?

Any part of the gut can be affected in Crohn's Disease. The most common area is the last part of the small intestine (terminal ileum) and the first part of the large intestine (or 'colon'), near the appendix[5]. In some people, only the colon is affected, in a pattern similar to ulcerative colitis. In others, multiple parts of the gut are affected. Rarely, the mouth, gullet or stomach may be involved. However, in some people, the inflammation in the gut also triggers inflammation outside the intestine leading to arthritis, eye inflammation or skin complaints.



HOW DOES CROHN'S AFFECT THE INTESTINE?

One form of Crohn's Disease results in patches of inflammation in the lining of the intestine with groups of small ulcers, similar to mouth ulcers. In moderate or severe Crohn's Disease, these ulcers become much larger and deeper with a lot of surrounding redness. The inflammation can make the intestine become thickened, blocking the passage of digested food. In some cases, deep ulcers break through the wall of the intestine causing infection outside the bowel (an abscess) and this can then spread to the skin or a nearby part of the body. This is known as a fistula. These most frequently occur around the anus. As the inflammation heals, scar tissue may form which can in some cases also lead to a blockage in the intestine.

WHAT ARE THE SYMPTOMS?

The main symptoms of Crohn's Disease are diarrhoea and abdominal pain. There may be some blood or mucus in the faeces, especially when the lowest part of the gut is affected. Digested food or faeces building up in narrowed or inflamed areas often occurring an hour or so after eating usually cause the pain. Sometimes, there is a tight blockage in the intestine causing severe, griping abdominal pain after eating, with swelling of the abdomen and vomiting. Losing weight is common when there is a lot of inflammation, as eating causes pain and many people with the condition feel excessively tired. Some people also have a temperature or sweats at night. There may also be sore, red eyes, swollen painful joints and skin rashes[3]. Some patients get perianal Crohn's disease which means that the inflammation occurs around the lower bowel and anus.

HOW IS IT DIAGNOSED?

When someone visits their doctor with symptoms of persistent diarrhoea and abdominal pain, they will try to decide whether special tests are needed to look for the possibility of Crohn's Disease and ulcerative colitis. There are many causes of diarrhoea in young adults including the irritable bowel syndrome (IBS), and infection (for example after travel abroad). The doctor will listen to the symptoms and ask about any of the related symptoms described above and also whether there is anyone in the family with Crohn's Disease or ulcerative colitis.

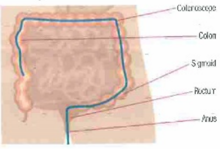
An examination will then find out if there are any signs of inflammation (such as tenderness in the abdomen or a lump) and whether there are any general signs of illness such as looking pale or underweight. A blood test might be arranged to see if there are changes in the blood which suggest inflammation[6]. If the doctor suspects that Crohn's Disease is a possibility, a referral will be made to a specialist for further tests.

WHICH TESTS ARE USED TO DIAGNOSE CROHN'S DISEASE?

The most frequent test used to diagnose Crohn's Disease is a colonoscopy. This involves the passage of a tube with a video camera at the end around the colon and, where possible, into the last part of the small intestine. Laxative preparation is needed before the examination to clear the bowel and allow good views of the lining of the intestine[7]. In most cases, sedation is given through a vein at the start of the procedure to minimise some feelings of discomfort associated with passage of the tube along the colon.

By doing this test, doctors can get very accurate pictures of the state of the lining of the intestine and take samples for examination in the laboratory. If the colon and last part of the small intestine are seen to be normal, Crohn's Disease is very unlikely to be present.

In some cases, other tests are also needed. For example, a barium follow through examination allows the whole of the small intestine to be shown. In this test, liquid barium is swallowed and X Rays are taken as it passes through the intestine. Increasingly, other methods are used; these include magnetic resonance imaging (MRI) or capsule endoscopy, where a 'radiopill' is swallowed and transmits pictures as it passes through the intestine. Scans such as ultrasound or CT scanning may be needed, especially if an abscess or problems on the outside of the intestine are suspected.



HOW IS CROHN'S DISEASE TREATED?

Treatments for Crohn's Disease aim to reduce or heal the inflammation in the intestine and to deal with the effects of the disease, such as weight loss, and any complications. The inflammation is generally treated with medicines but in some cases surgery is required to cut out very inflamed or narrowed sections of intestine.

Many patients ask whether they should change their diet, but there is no proven specific diet for Crohn's Disease. There are, however, diets for certain situations. The most frequent dietary change is a reduction in fibre and indigestible foods, which cause pain when there is a narrowing in the intestine (a 'low residue diet'). Specialised liquid formula diets ('elemental' or 'polymeric' diets) are also used as treatment in Crohn's Disease, especially when it affects the small intestine. These diets rest the bowel, improve nourishment and reduce inflammation and are used especially in children where maintaining growth and weight is very important.

Medicines used to treat Crohn's Disease are mainly directed at the immune system in the intestine.

- Antibiotics (such as metronidazole) can be helpful, either by reducing the bacteria which 'drive' the inflammation, or to treat abscesses. They are not used for long-term treatment.
- Aminosalicylates are a relative of aspirin and are used to treat milder inflammation or reduce the chances of recurrence (for example, after an operation). Not all patients are helped by these drugs.
- Steroids (prednisolone, hydrocortisone) are much stronger drugs used to suppress inflammation when the symptoms are more severe. Steroids are very effective (about eight out of ten patients have a good response) but have side effects such as weight gain, insomnia, infection and acne and prolonged use can result in thinning of the bones. Steroids are therefore only used as a short-term measure to get Crohn's Disease under control[4]. There is a newer form of steroid (budesonide) which has fewer side effects due to mostly acting within the gut itself[5].
- For long term steroid use, immunosuppressive drugs are often used to reduce inflammation over a longer period and allow steroids to be stopped. Azathioprine and 6-mercaptopurine are the most frequently prescribed and around two-thirds of patients have a successful response. Side effects can occur and patients on these drugs therefore need to have regular blood tests. On the whole, however, most patients tolerate the drugs well and they remain the most effective medicine for keeping Crohn's Disease under control.
- Methotrexate is another immunosuppressive drug, commonly used for treating rheumatoid arthritis. This is usually the next choice if azathioprine or 6-mercaptopurine have failed.

The strongest drug treatment used for Crohn's Disease involves 'biological therapy' in which specially developed antibodies are used to block the effects of the molecules that are involved in the inflammation in the gut wall. The best-known biological therapies target a substance called tumour necrosis factor (TNF)[6] and are given by a regular intravenous drip or an injection under the skin. Other similar treatments, which target different inflammatory mediators, are under development. These treatments are very effective but can also have side effects especially increased rates of infection and allergic reactions, so they are reserved for people with severe Crohn's Disease and when other medicines have not worked. They need to be used under care of hospital specialists.

Surgical operations are a very important part of the treatment of Crohn's Disease and it is estimated that as many as eight out of ten patients will require an operation at some stage in their life. The main reason for needing surgery is to remove thickened blocked segments of the intestine. Medicines are unlikely to help these and an operation to cut out a short section of affected intestine is usually very successful with few problems and restores full health quickly[8]. Sometimes, colonoscopy can be used to open up narrowed sections (with special dilating balloons) but this is only possible in certain cases. Surgery is also needed when badly affected parts of the intestine have caused an abscess or fistula. Such fisula can occur on the abdomen or in the perianal area. An operation can sometimes be the best option when severe Crohn's Disease is not responding to drug treatment.

DOES SURGERY MEAN HAVING A STOMA BAG?

Many people presume that surgery for Crohn's Disease means having a permanent stoma bag. In fact, stomas (ileostomy or colostomy) are not often needed and are nearly always a temporary measure[9]. After a section of affected intestine has been removed, a very delicate join (or 'anastomosis') is made between the unaffected ends of the intestine. In order to protect this join while it heals, the surgeon will often make a temporary stoma above, which is then taken away at a second smaller operation a few months later. This is done particularly when someone is underweight or taking steroids which reduce the ability of body tissues to heal.

DOES CROHN'S DISEASE COME BACK AFTER SURGERY?

Yes as there is no cure for Crohn's Disease so it does come back, often in the section of intestine just above a surgical join. However, despite this, most people have no problems for many years after their operation. Recurrence is two-times more likely in smokers compared those who do not smoke[10]. Drugs such as aminosalicylates or azathioprine can also reduce the chances of recurrence.

DOES CROHN'S DISEASE AFFECT MY CHANCES OF HAVING CHILDREN?

Overall, Crohn's Disease does not have a significant effect on the chances of becoming pregnant or carrying a baby[11]. In a small number of cases, inflammation or infection in the pelvis, or surgery to this area, can affect the ovaries, fallopian tubes or uterus reducing fertility. The commonly used drugs used in Crohn's Disease are safe during pregnancy. It is always best to talk to your specialist if you have Crohn's Disease and are planning a pregnancy or already pregnant.

CAN I EXPECT A NORMAL LIFE IF I HAVE CROHN'S DISEASE?

In most cases, Crohn's Disease does not have much impact on daily life, the ability to work or to enjoy an active social life, but does take some getting used to. When it is active, symptoms such as diarrhoea and abdominal pain often require time away from work, college etc and make it difficult to cope at home or go out. However, treatment usually makes the symptoms better within days or weeks so work and home life is restored quite quickly.

The chances of dying if you have Crohn's Disease are no different to if you don't have the disease[12]. There are many forums and support groups around for those who suffer from Crohn's Disease to join, help and find out more information from. One example is www.crohnsforum.com/

WHAT CAN BE DONE TO PREVENT CROHN'S DISEASE?

There is currently no evidence any particular change in diet or lifestyle can prevent Crohn's Disease. Not smoking, or stopping smoking, is perhaps the most important of all the things to do. Although not proven, it makes sense to eat a balanced healthy diet favouring freshly cooked food over processed foods.

WHAT RESEARCH IS NEEDED?

The cause of Crohn's Disease remains unknown. However, our understanding of how and why the condition develops is increasing all the time. In particular, researchers are looking into how the hereditary (genetic) aspects of Crohn's Disease might change the way the immune system in the intestine deals with bacteria and other dietary substances present at the surface of the gut. This is very important research and there is hope that it will, before too long, lead to much better treatments and maybe even a cure.

REFERENCES:

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142:46-54.e42; quiz e30.
2. ghr.nlm.nih.gov/condition/crohn-disease#genes
3. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci. 1989;
4. A Hollis, LA Dieleman, HW Verkema et al. Environment and the inflammatory Bowel Disease. Can J Gastroenterol 2013.
5. www.nhs.uk/Conditions/Crohns-disease/Pages/Symptoms.aspx
6. crohns.org.uk/crohns_disease/investigations-into-crohns-disease
7. crohns.org.uk/crohns_disease/drug-treatment
8. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Paul Rutgeerts. 1999
9. Surg Clin North Am. 2013 Feb;93(1):167-85. doi: 10.1016/j.suc.2012.09.002. Epub 2012 Oct 24. Surgical management of Crohn's disease. Lu KC, Hunt SR.
10. Yamamoto T. Factors affecting recurrence after surgery for Crohn's disease. World J Gastroenterol. 2005;11:3971–3979
11. International Journal of Gynecology & Obstetrics. Volume 58, Issue 2, August 1997, Pages 229–237. Fertility and pregnancy in inflammatory bowel disease. M Hudson, G Flett, TS Sinclair, BW Brunt, A Templeton.
12. World J Gastroenterol. 2012 April 21; 18(15): 1723-1731. Epidemiology and clinical course of Crohn's disease: Results from observational studies. Ebstein Hovde and Bjørn A Moum

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This leaflet was published by Core in 2014 and will be reviewed during 2016. If you are reading this after 2016 some of the information may be out of date. This leaflet was written under the direction of our Medical Director and has been subject to both lay and professional review.

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WHAT, WHY, HOW OR IF, WHEN

INFORMATION ABOUT

ULCERATIVE COLITIS

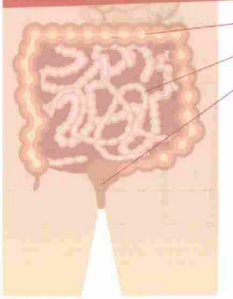
www.corecharity.org.uk

ULCERATIVE COLITIS

Ulcerative Colitis (UC) is a disease of the rectum and the colon (otherwise known as the large intestine). It is one of the two conditions that are known as Inflammatory Bowel Diseases (IBD) – the other being Crohn's Disease.

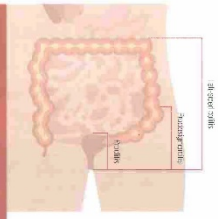
Any medical term that ends in –itis means that there is inflammation or damage to that part of the body. The term 'colitis' means the colon has become inflamed and, if this becomes severe enough, the lining of the colon can be breached and ulcers may form. The term 'ulcerative colitis' can seem confusing, as many patients never actually develop ulcers because the degree of inflammation is not that advanced. It's best to think of UC as a disease in which there is wide variation in the amount of inflammation so that in mild cases the colon can look almost normal but when the inflammation is bad, the bowel can look very diseased and can contain ulcers.

One study, from the UK, found that UC affects around 14 people per 100,000 with average incidence being around 10 per 100,000 people[1]. The peak age of incidence between 15-25 years old with a smaller peak occurring between the age of 55 and 65 years old but it can occur at any age[2]. It is more common in certain populations[3] (Ashkenazi Jews and South Asians).



HOW MUCH OF THE COLON CAN BECOME DISEASED?

Ulcerative colitis[4] always affects the rectum – that part of the large bowel, which lies just inside the anus. Sometimes the inflammation is limited just to the rectum, which is known as proctitis, as seen in the picture below. However, the inflammation can involve a variable length of the colon. When the whole colon is affected this is called pan-colitis or total colitis. We don't know why the amount of inflamed bowel varies so much between individuals.



WHY DOES UC HAPPEN?

We don't know the cause of ulcerative colitis – it is most likely to result from a combination of factors[5]. Doctors have looked hard to find either an infection or potential dietary causes, but have drawn a blank. For a while it seemed that ulcerative colitis might be one of the diseases where the body seems to be attacking itself. We now think that this is very unlikely, but there is no doubt that something must be causing damage to the lining of the large intestine.

Most doctors now think the cause of UC relates to how patients react to the apparently harmless bacteria that everyone has in their colon. In most people, the bacteria that live in the colon do not cause any damage and indeed can be quite useful. They are sometimes known as 'friendly' bacteria. However, patients with ulcerative colitis don't see them as being at all friendly and when the lining of the large intestine goes into battle with these bacteria, the result is that the inflammation starts[6]. An enormous research effort is under way to find out why patients with ulcerative colitis appear to react badly to bacteria that don't normally cause any harm in others.

WHAT ARE THE SYMPTOMS?

The three most common symptoms of UC are:

- Diarrhoea;
- Bleeding from the back passage;
- Pain in the abdomen.[7]

However, symptoms do vary from one patient to the next, so many people do not have all three of these together. For example, some patients may just notice that they pass blood when they open their bowels. Others may not have diarrhoea but feel rather constipated. To a certain extent, the symptoms depend on how much inflammation there is and how much of the colon is affected by the disease. Weight loss is a feature of severe disease.

For some people the symptoms can be a nuisance but may be tolerable. For others, the condition can really interfere with day-to-day life, which can become organized around visits to the toilet. It is not only just the number of times this can happen each day but the hurry in which some patients need a toilet can also be extremely distressing. As symptoms are often at their worst in the morning, this can mean the start of the day can be quite an ordeal.

Some patients pass considerable quantities of mucus when they open their bowels while others can be greatly troubled by wind. Many patients can just feel tired, not their usual self and they (or their family and friends) notice they have become just plain irritable. Sometimes there are symptoms outside the abdomen – such as sore eyes, painful joints and skin rashes.

WHAT IS YOUR DOCTOR LIKELY TO DO?

Doctors use three separate steps to come to a precise diagnosis. Firstly, they will listen to your symptoms and ask you questions about your health. This is called 'taking your history'. Secondly they will want to examine you to see if they can detect any 'signs' that something is wrong. For example, they may notice that you are unusually pale (which might suggest you are anaemic) or, perhaps, you seem rather tender when the doctor presses gently on your tummy (which can be a sign of inflammation in the colon). Thirdly, they will probably ask you to undergo some tests.

WHAT TESTS MIGHT I NEED?

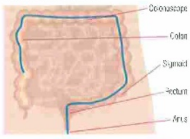
If your doctor thinks you might have ulcerative colitis, you will probably be asked to have tests of your blood, your motions and your intestines. Blood tests will show if you are anaemic and whether your illness has caused the level of protein to fall. In general, the greater the degree of anaemia and the lower the protein level, the more severe the inflammation is likely to be. Doctors also use special blood tests called ESR and CRP to give a measure of the degree of inflammation. You may be asked to give small samples of your bowel motions so as to be sure there are no signs of any bowel infection.

WHAT OTHER INVESTIGATIONS COULD BE NECESSARY?

The most important investigation is to look directly at the lining of the large intestine. Sometimes the doctor will choose to carry out such an examination in the outpatient clinic. This is known as sigmoidoscopy and has the convenience of you not having to take any special preparations beforehand as the doctor will only look at the rectum and perhaps the lowest part of the sigmoid colon. Sometimes biopsies (tiny pieces of the lining of the bowel) are taken at the time of sigmoidoscopy and analysed under a microscope in a laboratory. However, sooner or later, the doctor will want to see more of your bowel and the best way to do this is by the technique of colonoscopy.

WHAT IS A COLONOSCOPY?

A colonoscope is a tube which is long enough but sufficiently flexible to be passed through your back passage along the whole length of the colon. You will be asked to follow a special diet and also to take some quite powerful laxatives just before the test to make sure the bowel is entirely empty. You will be offered an injection beforehand to minimise any discomfort that might be caused – but an anaesthetic is only needed very rarely. It is usually possible to see all of the rectum and the colon and it is likely that the doctor will take some biopsies to study after the procedure has finished. A colonoscopy will confirm the diagnosis of ulcerative colitis and provide detailed information on the extent and severity of inflammation in the intestine. Biopsies are often used to confirm this diagnosis.



WHAT TREATMENT MIGHT I EXPECT?

Since the cause of ulcerative colitis is not known there are two important implications for treatment. Firstly, until the cause is discovered it is most unlikely that there will be a medicine that will cure the condition. Secondly, all treatments available at present are directed towards reducing the amount of inflammation in the bowel.

Fortunately, for most patients with UC medicines prove effective although it is possible that your treatment may need to be varied to find the drugs that work best for you. Your doctors will firstly try to find a treatment that will bring the disease under control. Then they will work on finding a treatment to keep you that way.

BRINGING ULCERATIVE COLITIS UNDER CONTROL

Your doctor may refer to this phase as "Putting your disease in to remission" and almost always, the choice of treatment will depend on the extent and severity of the inflammation within the large bowel. If the inflammation is confined to the rectum ('proctitis'), it is quite possible the doctor will recommend a medication that you will need to insert into the rectum through the back passage. Although the thought of this can be unpleasant, it can be helpful to appreciate that giving your treatment this way does mean that the therapy is accurately directed right against the inflamed part of your bowel. Treatment can be given as suppositories or as enemas. Enemas can also be useful if the disease involves more of the large bowel than just the rectum alone, but if the inflammation in the bowel is extensive enough to affect more than half of the colon, it is also likely that you will be prescribed tablets to take by mouth. There are some special dietary measures[7] that can be undertaken that may prevent relapses and be beneficial to UC patients such as limiting dairy intake and taking fish oils.

WHAT DRUGS ARE AVAILABLE?

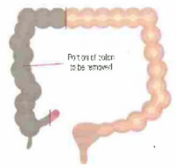
The anti-inflammatory drugs include aminosalicylates in milder cases and steroids if the inflammation is more severe. There are a variety of aminosalicylates (such as mesalazine8) and your doctors will choose the preparation they feel is best for you. They are usually extremely safe to use. Steroids (such as prednisolone[9]) are more powerful but doctors are rather reluctant for patients to take these drugs for more than a few weeks at a time because of the risk of side effects. However, most patients do get better with these treatments.

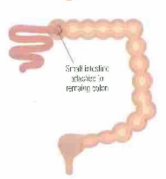
HOW MIGHT A RELAPSE BE PREVENTED?

Your doctor will discuss alternative ways of preventing relapse[10] and good control of your condition will depend on a partnership between you, your GP and your Specialist. Regular review is important to ensure that you are on the best possible treatment and that your symptoms are well controlled. Aminosalicylates are helpful and may reduce cancer risk. If possible, doctors try to avoid giving patients with UC steroids in the long term because of the side effects. As an alternative, the possibility of taking azathioprine may be discussed with you. This calms down the immune system and, although only weakly effective against active disease, it has proved most useful in preventing relapses. This drug does need close monitoring in the first few weeks of treatment in order to detect side effects although most people do not have any problems when they take it.

WHAT WILL HAPPEN IF TREATMENT WITH MEDICINES FAILS?

Doctors try hard to control UC with drugs and medicines. But in the occasional situation that these don't help or should you become very unwell, you may be offered admission to hospital[11]. If the disease still fails to respond to treatment, it is likely that a surgical operation to remove part or all of the colon (called a colectomy) will be considered. Although surgery can seem a drastic step, it does cure the disease (if you don't have a colon, you can't have colitis). In former times, colectomy used to mean needing a bag to wear on your tummy. Nowadays, it is usually possible to remove the diseased colon and rectum and then construct a pouch of small intestine that acts very much like the rectum giving no need for a bag.





CAN ULCERATIVE COLITIS CAUSE COMPLICATIONS?

A small number of patients do have complications that relate to UC in their skin, eyes, joints or liver as a result of their disease. When you attend the hospital, you will be monitored to see if any of these complications do develop so that they can be treated. You may have heard that patients with UC run an increased risk of getting bowel cancer[12]. The bad news is that this is true; the good news is that bowel cancer is still an uncommon complication of the disease and that your doctor will keep an eye on your bowel (quite literally; by performing colonoscopy at regular intervals) to detect pre-malignant changes in the lining of the bowel at a stage well before cancer has yet developed.

AM I LIKELY TO DIE OF THIS DISEASE?

No.

WHAT RESEARCH IS NEEDED?

We must find the cause of the disease. Until then, we need to know as much as possible about all the steps that lead the inflammation in UC to develop. This will lead to the development of better drugs to control the condition. Being able to target drugs directly against the causes of the inflammation in UC is proving to be very valuable in developing new treatments.

The Crohns and Colitis UK group have many detailed leaflets on living with UC (and Crohns) especially related to employment, disability and fertility. They also provide information about patient groups and volunteering opportunities. These are found at **www.crohnsandcolitis.org.uk**.

REFERENCES:

1. Ulcerative Colitis. Silvio Danese, M.D., and Claudio Fiocchi, M.D. N Engl J Med 2011; 365:1713-1725
2. Basson M et al. Ulcerative Colitis, Medscape. May 2011
3. Manguso et al Can J Gastroenterol. 2011 February 25(2): 73-77
4. www.nhs.uk/conditions/ulcerative-colitis/Pages/Introduction.aspx
5. Sands B Gastroenterology Clinics of North America (1995. 24(3):475-507)
6. www.patient.co.uk/health/ulcerative-colitis
7. www.ulcerativecolitis.org.uk/dietarychanges.htm
8. www.ulcerativecolitis.org.uk/medications/asacol_mesalazine.htm
9. www.ulcerativecolitis.org.uk/medications/steroids.htm
10. publications.nice.org.uk/ulcerative-colitis-cg166/key-priorities-for-implementation#inducing-remission-step-1-therapy-for-mild-to-moderate-ulcerative-colitis
11. Mowat C, Cole A, Windsor A, et al. Gut (2011). doi:10.1136/gut.2010.224154
12. www.cancerresearchuk.org/cancer-help/type/bowel-cancer/about/risks/high-risk-groups-for-bowel-cancer

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Our Vision To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS Foundation Trust

University of East Anglia

DELEGATION LOG

(Site signatures and delegation of responsibility log)

Study:	N-ASPIRE Tool
Principle investigator:	Chong Seng Edwin Lim
Site:	Norfolk and Norwich University Hospital

Legend		
Use this legend to complete the General Duties column. For each individual listed in the Name column, enter the letter(s) (eg, a c, e) from the legend below that correspond to their protocol-related duties in the General Duties Column. If there are significant protocol related duties that are not already included in the legend, add them in the empty spaces provided below.		
A. Identifying participant, providing/verifying IBD specific data for consented enrolled patients	B. Phase 1 activities – receipt and processing of returned questionnaires, data entry in electronic database	C. Phase 2 activities – checking eligibility criteria, telephone contact & invitation, informed consent process, clinical assessment, request of investigations, review & interpretation of results, data entry in paper and electronic database
D. Process of Physician Verified Diagnosis (PVD) and familiarisation with Rheumatologist Diagnosis Sheet (RDS)	E.	F.

Name (please print)	Trial Role	General Duties (see legend)	Initials	Signature	Date of Duties		Principal Investigator Signature	Date of PI Signature
					From (dd-MMM-yyyy)	To (dd-MMM-yyyy)		

Statement					
I have reviewed the information on this log and have found it to be accurate. All delegated duties were performed with my authorisation.					
Principle Investigator Signature:		Site Start Date:		Site End Date:	

The Bath Ankylosing Spondylitis Global Score (BAS-G)

	TOTAL / 10
How have you been over the last week? VERY GOOD _____ VERY BAD **How have you been over the last six months?** VERY GOOD _____ VERY BAD	
TOTAL OUT OF 20	
TOTAL / 2 (BAS-G SCORE)	

BAS-G Score
Scores from the 2 questions are calculated using a ruler and added. This figure is divided by 2 to obtain an average, this is the BAS-G score. The higher the BAS-G score, the more severe the effect of AS on the patient's life.

Please Note:
When using visual analog scales of a set length (10cm in the case of the Bath Indices), great care must be taken in reproducing assessment paperwork as repeated photocopying, for example, may distort the length of the lines and therefore will affect the accuracy of the scoring.

Referrence: Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 1996 Jan;35(1):66–71.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

a **If you are currently taking medication for your AS, please give the name and dose that is on the bottle/packet.**

b **Please mark on the line below to indicate the effectiveness of the medication in relieving your symptoms.**

NO EFFECT _____ VERY EFFECTIVE

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *past week*

		SCORE/10
1	**How would you describe the overall level of fatigue/tiredness you have experienced?** NONE _____ VERY SEVERE	
2	**How would you describe the overall level of AS neck, back or hip pain you have had?** NONE _____ VERY SEVERE	
3	**How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?** NONE _____ VERY SEVERE	
4	**How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?** NONE _____ VERY SEVERE	
5	**How would you describe the overall level of discomfort you have had from the time you wake up?** NONE _____ VERY SEVERE	
6	**How long does your morning stiffness last from the time you wake up?** _____ 0 ½ 1 1½ 2 or more hours	
	MEAN OF 5&6	
	TOTAL OF 1 TO 4 ADDED TO MEAN OF 5&6 (TOTAL OUT OF 50)	
	TOTAL / 5 (BASDAI SCORE)	

BASDAI Score Calculation

Score from all questions are calculated using a ruler. The mean measurement (score) of questions 5 and 6 is added to the scores from questions 1 to 4. This total is then divided by 5 to give the average. This is the BASDAI score. The higher the BASDAI score, the more severe the patients disability due to their AS.

Please Note:
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Referrence: Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994 Dec;21(12):2286–91.

The Bath Ankylosing Spondylitis Functional Index (BASFI)

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *past week*

HOW DO YOU FIND:	score out of 10
1 Putting on your socks or tights without help or aids (eg sock aid)? EASY _____ IMPOSSIBLE	
2 Bending forward from the waist to pick up a pen from the floor without an aid? EASY _____ IMPOSSIBLE	
3 Reaching up to a high shelf without help or aids (eg Helping Hand)? EASY _____ IMPOSSIBLE	
4 Getting out of an arm-less dining chair without using your hands or any help? EASY _____ IMPOSSIBLE	
5 Getting up off the floor - without help - from lying on your back? EASY _____ IMPOSSIBLE	
6 Standing unsupported for ten minutes without discomfort? EASY _____ IMPOSSIBLE	
7 Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)? EASY _____ IMPOSSIBLE	
8 Looking over your shoulder without turning your body? EASY _____ IMPOSSIBLE	
9 Doing physically demanding activities (eg physio exercises, gardening, sport)? EASY _____ IMPOSSIBLE	
10 Doing a full day's activities at home or at work? EASY _____ IMPOSSIBLE	
TOTAL OUT OF 100	
TOTAL / 10 (BASFI SCORE)	

BASFI Score Calculation

Score from all questions are calculated using a ruler and added. This figure is divided by 10 to obtain an average. This is the BASFI score. The higher the BASFI score, the more severe the patient's limitation of function due to their AS.

Please Note:
When using visual analog scales of a set length (10cm in the case of the Bath Indices), great care must be taken in reproducing assessment paperwork as repeated photocopying, for example, may distort the length of the lines and therefore will affect the accuracy of the scoring.

Reference: Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994 Dec;21(12):2281–5.

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

University of East Anglia

TRAINING LOG
(Including Delegation Checklist)

Study:	N-ASPIRE Tool
Principle investigator:	Chong Seng Edwin Lim
Site:	Norfolk and Norwich University Hospital

Training Topics / Checklist
1. Curriculum vitae (CV)
2. Good Clinical Practice (GCP)
3. Review of Study Protocol
4. Identifying participant and providing/verifying IBD specific data for consented enrolled patients
5. Phase 1 activities – receipt and processing of returned questionnaires, data entry in electronic database
6. Phase 2 activities – checking eligibility criteria, telephone contact & invitation, informed consent process, clinical assessment, request of investigations, review & interpretation of results, data entry in paper and electronic database
7. Process of Physician Verified Diagnosis (PVD) and familiarisation with Rheumatologist Diagnosis Sheet (RDS)
8. Other (write in):
9. Other (write in):
10. Other (write in):

Method of Training / Evidence	
1. Document(s) showing previous achievement as evidence	5. Self Study – Additional protocol specific summary materials
2. Live Training & Coaching by PI	6. Other (Explain):
3. Self Study – Paper protocol review	7. Other (Explain):
4. Self Study – Electronic protocol review	8. Other (Explain):

Name and Title of Trainee	Trainee initials, signature and date	List of topics numbers covered during training	Method of training	Comments (e.g. Date of CV & GCP, etc)	Confirmation by PI (initials & date)

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email: eleanor.sykes@nnuh.nhs.uk

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label or Type in template

Axial Spondyloarthritis in Inflammatory Bowel Disease – secondary care cross-sectional prevalence and development of an evidence-base referral tool [Norfolk - axial SpA IBD referral Tool (N-ASPIRE Tool)]

Dear (Insert Patient's Name),

Insert Appropriate Details e.g. appointment details, result letter, etc

Yours sincerely,

Dr Chong Seng Edwin Lim
Senior Research Fellow (Rheumatology)

Dr Karl Gaffney
Rheumatology Consultant

2. Protocol of the N-ASPIRE Imaging Strategy Study

Our Vision To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS NHS Foundation Trust

UEA University of East Anglia

N-ASPIRE CT Strategy Protocol	
What proportion of patients with Inflammatory Bowel Disease have Axial Spondyloarthritis – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis [Norfolk - Axial SPa Ibd REferral Computed Tomography Strategy (N-ASPIRE CT Strategy)] N-ASPIRE CT Strategy	
Chief Investigators	Dr Chong Seng Edwin Lim MBBS, MRCP (UK) (Rheumatology) Senior Research Fellow (Post-CCT) Norfolk and Norwich University Hospital
Support / Funder	AbbVie
Sponsor	Norfolk & Norwich University Hospital NHS Foundation Trust (NNUH) – Lead Sponsor University of East Anglia (UEA) – Co-sponsor
Document type	Final Protocol
Version number	2.0
Date	25th April 2019
This protocol does not have regard to the HRA guidance and order of content	

Protocol Version

Document type	Version No.	Version Date	Person	Reason
Final	1.0	06/02/19	Dr CSE Lim	Initial
Final	2.0	25/04/19	Dr CSE Lim	Amendments

Study Identifier

R&D / Sponsor Reference Number	252117 (133-10-18)
Support / Funder Reference Number	SA-001966
IRAS Project ID Number	252117
REC Reference Number	19/EE/0125
International Standard Randomised Controlled Trial Number (ISRCTN)	ISRCTN11108086 http://www.isrctn.com/ISRCTN11108086

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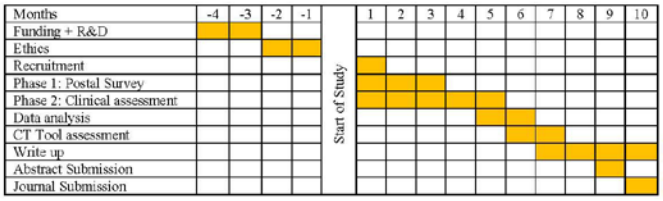
List of Abbreviations & Definitions

AAU	Acute Anterior Uveitis
AP	Anteroposterior
AS	Ankylosing Spondyloarthritis
ASAS	Assessment of Spondyloarthritis International Society
axPsA	Axial Psoriatic Arthritis
axSpA	Axial Spondylcarthritis
AS	Ankylosing Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASG	Bath Ankylosing Spondylitis Global score
BASMI	Bath Ankylosing Spondylitis Metrology Index
CBP	Chronic Back Pain
CCT	Certification of Completion of Training
CD	Crohn's Disease
CI	Confidence Interval
CI	Chief Investigator
CORE	Fighting Digestive Diseases
CRF	Case report form
CRP	C reactive protein
CT	Computed Tomography
CTASJ	Computed Tomography defined Abnormal Sacroiliac Joint
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTSI	Computed Tomography defined Sacroilitis
Dx	Diagnosis
EAM	Extra-Articular Manifestations
ESR	Erythrocyte Sedimentation Rate
ESSG	European Spondyloarthropathy Study Group
GCP	Good Clinical Practice
GP	General Practitioner
HLA-B27	Human Leucocyte Antigen B27
IBD	Inflammatory Bowel Disease
IBP	Inflammatory back pain
ICE	Integrated Clinical Environment
MSK	Musculoskeletal
MST	Multi-Specialist Team
mNYC	Modified New York Criteria
MRI	Magnetic Resonance Imaging
NASS	National Ankylosing Spondylitis Society
NHS	National Health Service
NNUH	Norfolk & Norwich University Hospital
nr-axSpA	non-radiographic axial spondyloarthritis
NSAIDS	Nonsteroidal Antiinflammatory Drugs
PCF	Participant Consent Form
PI	Principle Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PROMS	Patient report outcome measures
PsSpA	Psoriatic Spondyloarthropathy/Spondyloarthritis
R&D	Research and Development
rad-axSpA	Radiographic Axial Spondyloarthritis
RDS	Rheumatologist Diagnosis Sheet
REC	Research Ethics Committee
RSI	Radiology Imaging System

RVD	Rheumatologist Verified Diagnosis
SIJ	Sacroiliac joint
SOP	Standard Operating Procedure
SQ	Screening Questionnaire
TNF	Tumour Necrosing Factor
X-ray	Radiograph / Radiographic
UC	Ulcerative Colitis

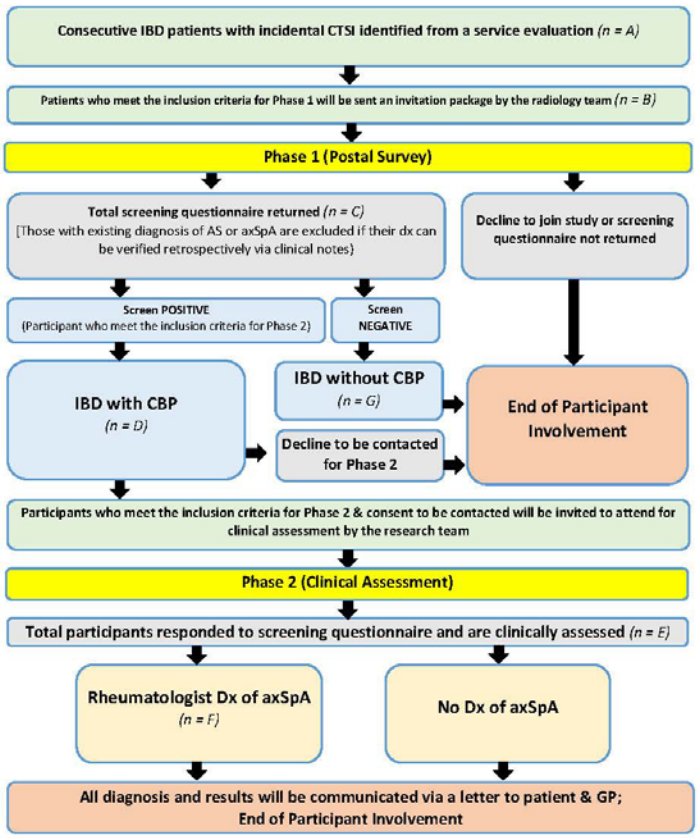
Table of Contents

1. Study Summary

Title	What proportion of patients with Inflammatory Bowel Disease (IBD) have Axial Spondyloarthritis (axSpA) – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis (CTSI) [Norfolk - Axial SPa Ibd REferral Computed Tomography Strategy (N-ASPIRE CT Strategy)]
Acronym	N-ASPIRE CT Strategy
Study aims and objectives	1. To estimate what proportion of IBD patients with incidental CTSI (undertaken for non-musculoskeletal (MSK) indications) have axSpA. 2. To assess the utility of a CT screening tool to facilitate the identification of axSpA – the N-ASPIRE CT Strategy.
Study Design	Investigator led, single centre, observational (cross-sectional), non-interventional study
Study Site	Norfolk & Norwich University Hospital
Study Duration	10 months from study commencement date
Study Timeline	
Sample Size	54 subjects (minimum number of CTSI needed to be screened)
Study Population	Adults aged 18-55 with IBD, identified with incidental CTSI from a service evaluation.
Primary outcomes	• Proportion of IBD patients with incidental CTSI who have a rheumatologist verified diagnosis of axSpA.
Secondary outcomes	• Proportion of patients who fulfil the ASAS classification criteria for axial axSpA • Proportion of symptomatic vs asymptomatic incidental CTSI

1.1 Study Flow Chart

Figure 1 – Study Flow Chart



2. Introduction

2.1 Background

AxSpA is a chronic inflammatory arthritis predominantly involving the spine and sacroiliac joints, with or without extra-spinal MSK manifestations (peripheral arthritis, enthesitis, dactylitis) and extra-articular manifestations (acute anterior uveitis (AAU), psoriasis and inflammatory bowel disease) (1). AxSpA has a disease spectrum. This includes *non-radiographic axSpA* – individuals with axSpA features but without established radiographic changes, and *radiographic axial spondyloarthritis* (commonly known as Ankylosing Spondylitis (AS)) – individuals with axSpA features and radiographic sacroiliitis (2).

AxSpA is diagnosed clinically based on suspicious clinical features supported by laboratory tests (Human Leucocyte Antigen B27 (HLA-B27), raised C-reactive protein (CRP)) and imaging (Magnetic Resonance Imaging (MRI) and/or X-ray). Advances in MRI have enabled earlier diagnosis of axSpA via the identification of bone marrow oedema compatible or highly suggestive of axSpA in the sacroiliac joints and/or spine prior to the development of structural changes on radiographs (3–7). Classification criteria for axSpA (see Figure 1) based on a combination of imaging or clinical criteria in patients with chronic back pain with onset before 45 years of age has been developed by the Assessment of SpondyloArthritis international Society (8,9). These are useful for research purposes but are not diagnostic criteria.

Figure 1 – ASAS Classification Criteria for Axial Spondyloarthritis (axSpA) (9)

<table>
<tr><td colspan="3">In patients with >3 months of back pain and age at onset < 45 years old</td></tr>
<tr><td>Sacroiliitis on imaging * AND
≥1 SpA feature**</td><td>OR</td><td>HLA-B27 AND
≥2 other SpA features **</td></tr>
<tr><td colspan="2"><u>** SpA features:</u>
• Inflammatory back pain
• Arthritis
• Enthesitis (heel)
• Uveitis
• Dactylitis
• Psoriasis
• Crohn's/Colitis
• Good response to NSAIDS
• Family history for SpA
• HLA-B27
• Elevated CRP</td><td><u>* Sacroiliitis on imaging:</u>
• Active acute inflammation on MRI highly suggestive of sacroiliitis associated with SpA
• Definite radiographic sacroiliitis according to modified New York criteria</td></tr>
</table>

AxSpA typically begins in the 2nd and 3rd decade (10). Delay to diagnosis is a major problem with an average delay of between 8-10 years. This means that patients often endure intolerable symptoms, linked to worse outcomes (disease activity, function, radiographic), despite the availability of effective new therapies (11). Early treatment offers the best chance of drug free remission and early disease responds best to TNF inhibitors (12,13). Sykes et al (14) have

recently shown that the delay to diagnosis has not improved despite the advances in modern imaging and new approaches to diagnosis. They divided 1193 patients with a rheumatologist-verified diagnosis of axSpA into a historical (diagnosed pre-2009) and current cohort (diagnosed 2009-2013) and found that the mean delay to diagnosis in the historical cohort was 8.53 years, and 9.39 years in the current cohort. They concluded that there is still a need for further targeted education of health-care professionals in order to address the issue of delay to diagnosis.

There is a close association between IBD and the axSpA disease spectrum. This is evident from previous and emerging literature in epidemiology, imaging and genetics. The estimated prevalence of AS in IBD patients is between 1% to 25%, with a recent calculated pool prevalence of 3% (15). The prevalence range varies considerably and is reported to be between 4% to 7% in axSpA (16,17). Radiographic sacroiliitis (symptomatic and asymptomatic) is common, reported to be prevalent in IBD patients between a range of 1% to 45% (18) with a recent calculated pooled prevalence of 10% (15). In addition, there is increasing evidence from genome-wide association studies that there is a relationship between AS and gut inflammation which may explain the close association of the two conditions. Shared genetics may contribute to a common inflammatory pathway (19,20).

Clinical referral strategy trials have been proposed to facilitate identification of axSpA but almost all are primary care referral strategies based on a combination of inflammatory back pain, imaging findings, HLA-B27 results and associated clinical features (21) (4) (22) (23). In secondary care referral strategies, Haroon et al's group in Ireland and Sykes et al (from our institution, NNUH) have recently investigated pathways for direct AAU referrals to rheumatology for assessment (24,25). As IBD patients tend to undergo imaging evaluation for various assessments of their gastrointestinal disease, there may be an opportunity to utilise existing scans to trigger further assessment for the diagnosis of axSpA in those with suspected sacroiliitis.

CT is one method for identifying sacroiliitis. Recent evidence have shown that the prevalence of sacroiliitis in CT done in patients with IBD for non-MSK indications is between 2.2% and 25% in non-UK institutions (26–29). Identifying imaging sacroiliitis is an important component of both rheumatologist verified diagnosis and axSpA classification. However, sacroiliac joint abnormalities can vary with age and cause, so it is important to take clinical context into consideration (30,31). In axSpA, CT changes suggest structural (post-inflammation) changes. The spectrum of abnormal sacroiliac joint changes may vary with disease duration and disease phenotype (32–34). There have been recent efforts in using a CT screening tool to differentiate sacroiliitis in (i) AS and controls (35) and (ii) IBD and controls (29). However, there are no studies in the literature reporting what proportion of IBD patients, identified with CT imaging sacroiliitis suggestive of axSpA/AS, will actually have a rheumatologist verified diagnosis of axSpA.

2.2 Rationale

It is good practice and routine practice that IBD patients with incidental CTSI suspicious of axSpA should be referred to rheumatology and have a clinical assessment (including a MRI scan in the modern diagnostic workup of axSpA) to verify the diagnosis of axSpA. However, there is evidence that this is not being undertaken (29).

We propose that it is important to understand the "hidden burden" of axSpA in this population. We will also explore the utility of a screening tool (35) as an adjunct to help improve imaging interpretation in the onward management of incidental CTSI. This may be an additional strategy to identify undiagnosed axSpA in the IBD population by the utilising existing CT scans which have been undertaken for non-MSK indications. This is in line with recent research recommendation from the National Institute for Health and Care Excellence (NICE) guidance NG65 on axSpA calling for evidence in IBD specific-referral rules (36). This approach may reduce healthcare utilisation costs, reduce delay to diagnosis, and facilitate access to available effective treatments.

3. Aims and Objectives

3.1 Aims

A single centre prospective observational non-interventional usual-standard-of-care study to estimate what proportion of axSpA in existing secondary care IBD population who have incidental CTSI seen on a pre-existing CT scan imaging done for non-MSK indications and the assessment of the utility of a validated CT screening tool to facilitate the identification of axSpA in symptomatic incidental CTSI patients.

3.2 Objectives

1. To estimate what proportion of IBD patients with incidental CTSI (undertaken for non-MSK indications) have axSpA.
2. To assess the utility of a CT screening tool to facilitate the identification of axSpA – the N-ASPIRE CT Strategy.

3.3 Primary Outcomes

- Proportion of IBD patients with incidental CTSI who have a rheumatologist verified diagnosis of axSpA.

3.4 Secondary Outcomes

- Proportion of patients who fulfil the ASAS classification criteria for axSpA
- Proportion of symptomatic vs asymptomatic incidental CTSI

4. Study Design

4.1 N-ASPIRE CT Strategy study description

The study includes:

1. A postal survey of patients with IBD in secondary care who have been identified with incidental CTSI on a pre-existing CT done for non-MSK indications
2. A structured assessment (undertaken by a group of experienced rheumatologists) of a subset of participants (those with chronic back pain) in order to establish what proportion of these participants have axSpA.

The study will consist of two phases outlined below (Section 4.2 to 4.6).

4.2 Phase 1: Postal survey

Recruited subjects meeting the inclusion criteria for phase 1 (See Section 5.1) are sent an invitation package. The screening questionnaire is a modification of a validated questionnaire by Hamilton et al (37).

The invitation package contains:

1. Invitation cover letter by the radiology team (See Appendix A)
2. Participant Information Sheet (PIS) (See Appendix C)
3. Screening Questionnaire (SQ) (See Appendix F)
4. NNUH Magnetic Resonance Imaging (MRI) Patient Information (See Appendix I)

A second invitation letter is sent out after one month. A prepaid return envelope will be provided with the invitation package.

4.3 Phase 2: Clinical assessment

Subjects who have completed phase 1 and meet the inclusion criteria for phase 2 will then be invited to attend a clinic appointment at the rheumatology department for clinical assessment if they have given consent to be contacted in the screening questionnaire.

Formal consent will be obtained at the clinic appointment. The clinical assessment carried out including the biochemical and imaging investigations are routine standards of care for any patient with a suspected diagnosis of axSpA in NNUH. Clinical assessment will include a structured history, structured physical examination and rheumatological outcome measurements using a paper Case Report Form (CRF). Laboratory tests will include HLA-B27, CRP and ESR using the trust's standard routine pathology protocol. Imaging studies will include an MRI using the trust's axSpA imaging protocol. A rheumatologist verified diagnosis (RVD) will be made via virtual Multi-Specialist Team (MST) meetings.

The final RVD and results of the investigations will be communicated to the patient and their GP via a formal letter. This will include an interpretation of test results and diagnosis. The letter will also include a recommendation that participants discuss the findings with their GP. It will be stated clearly that the letter will be copied to their GP, so that their GP is aware of

their individual outcome of the study. The patient's subsequent care will be directed by the participant's general practitioner and their trial involvement will then end.

Subjects will receive reimbursement for reasonable travel expenses (based on car mileage or train/bus ticket) up to a maximum of £10 pounds per subject per visit. No additional payments or incentives above the travel expenses will be offered.

Subjects who are unable to complete the Clinical assessment, Laboratory test or MRI will be will not continue with Phase 2. A letter communication will be sent to the patient and their GP, and their trial involvement will then end.

Subjects who have completed phase 1 and do not meet the inclusion criteria for phase 2 will have their data included in the "IBD without chronic back pain" group if consent was given in their screening questionnaire. All subjects NOT invited for a clinical assessment will be sent a letter of appreciation (See Appendix B) and their study involvement will then cease.

4.4 Imaging Protocol

This is the imaging protocol used in NNUH for any patients with a suspected diagnosis of axSpA.

The technical language of the trust's standard imaging protocol for MRI axSpA protocol is "Sagittal T1 Lumbar(L)-spine, Sagittal T2 Fatsat L-spine, Axial T2 L-spine as appropriate, Sagittal T1 Thoracic(T)-spine, Sagittal T2 Fatsat T-spine, Axial T2 T-spine as appropriate, Coronal oblique T1 SIJ, Coronal oblique T2 Fatsat SIJ".

4.5 Interpretation of results

All results will be treated as "real world" routine clinical practice. HLA-B27 status is either positive or negative as provided in the lab report. CRP and ESR are abnormal if they are outside the laboratory reference range. The MRI of the sacroiliac joints and spine will be undertaken using a standardised axSpA protocol and will be interpreted by an experienced MSK radiologist and reported as per routine clinical practice. Any discrepancies will be discussed in the weekly radiology multidisciplinary meeting and agreement will be by consensus majority. A "positive MRI" will also be defined using the ASAS 2009 MRI definition (7) with its recent update and guidance (6). A positive spinal MRI for inflammation will be established according to guiding reference with the ASAS-OMERACT 2012 definition (38).

4.6 Rheumatologist verified diagnosis of axSpA

Each subject will be discussed in a virtual MST meeting, an initial discussion solely based on clinical history and examination findings and re-discussed following the availability of laboratory and imaging results.

The MST will be made up of a panel of 3 expert rheumatologists with a specialist interest in axSpA of varying experience (post-CCT research fellow, junior consultant and senior consultant) to simulate real world situation. Clinical data of each patient will be presented as per "raw data" collected in the CRF. After discussion of the clinical data, each rheumatologist will make either a positive or negative diagnosis of axSpA and indicate the level of confidence

of the diagnosis on a 10-point Likert scale on the Rheumatologist Diagnosis Sheet (RDS; See Appendix H).

The definition of a RVD in this study is when a positive axSpA diagnosis is made by 2 of 3 rheumatologists and the level of confidence will be reflected by the average of the three Likert scale. A similar process will follow when the results of imaging and laboratory results are made known to them. Any discrepancy between the pre- and post- investigation revelation RVD will be discuss in the MST and a final RVD made by a majority consensus vote of 2 of 3 rheumatologists. An alternative diagnosis for subjective symptoms will be suggested when no final RVD of axSpA is made. Details of the findings of the sacroiliac joints on previous CT scans during the service evaluation are blinded to the MST until a final RVD is made and at the analysis stage of the study.

5. Study Population

The study population will be patients with existing IBD who have incidental CTSI of their sacroiliac joints identified on CT performed for non-MSK indications in a single university hospital (NNUH)

5.1 Inclusion criteria for Phase 1 (Postal Survey)

- CT scan performed for non-MSK indications
- Age between 18 and 55 years old inclusive at the time of CT scan. Almost all cases of disease would be captured if symptom onset is chosen at or before 45 years old (39). Given the diagnostic delay window of approximately 8-10 years (14,31), the age range of 18 to 55 years old was chosen as one which will be of highest diagnostic yield
- Verified IBD diagnosis (by gastroenterologist via gastroenterology clinical letter +/- supportive histology / radiology results using electronic medical, lab, radiology records)
- Presence of incidental CTSI which is defined as the presence of sacroiliac joint ankylosis or total erosion score (TES) of $\geq$3 or > 0.5 cm iliac sclerosis or > 0.3 cm sacral sclerosis from current literature (35). We selected the criteria with the highest sensitivity (94%) as this sample is already an enriched population (IBD diagnosis & age range with the highest diagnostic yield)

5.2 Inclusion criteria for Phase 2 (Clinical assessment)

- Chronic back pain (> 3 months)
- Onset of back pain before 45 years old
- Including known/previous diagnosis of AS or axSpA (if unable to verify diagnosis retrospectively)

5.3 Exclusion criteria

- Unable to tolerate MRI scanning (e.g. current history of claustrophobia) unless excepting of sedation as per routine clinical practice or contra-indication to MRI scanning (including but not limited to e.g. pacemaker, pregnancy, metallic or conducting foreign body, etc.)
- Age <18 or >55 years
- Patients lacking in capacity and/or unable to give informed consent
- Patients unable to understand English to sufficient degree to be able to complete a questionnaire
- Illiteracy
- Prisoners
- Patients unwilling to take part in the study

6. Recruitment and Enrolment

6.1 Identifying participants

Patients are identified using a combined radiology-rheumatology service evaluation project. Patients with incidental CTSI identified in patients with IBD performed for non-MSK indications are obtained from a service evaluation project. This service evaluation was undertaken to explore the standards of sacroiliac joint reporting in patients with existing IBD who had CT scans undertaken for non-MSK indications at the Norfolk and Norwich University Hospital.

6.1.1 Summary of Service Evaluation Project

The characteristics of this sample were:

- CT abdomen, CT pelvis, CT abdomen-pelvis done in patients with "colitis", "Crohn*", "inflammatory bowel disease", "IBD", were identified from the radiology imaging system (RIS) retrospectively
- The resulting results were filtered to the population with the highest diagnostic yield i.e. 18-55 years old (14,30,31)
- The resulting scans were then cross-referenced with the electronic clinical letters and histology/radiology results to ensure that only existing IBD patients were included. IBD patients are patients with a Gastroenterology diagnosis of Crohn's disease or Ulcerative Colitis, supported by endoscopic/histological or radiological reports/statements.
- If there were multiple scans, the most recent CT scan was used as the INDEX scan for review and analysis

- Time frame of search was from Jan 2010 to Dec 2017 (8 years). We tried to include all eligible patients and this was the maximum time frame where the RIS was index accurately.
- Scans were reviewed by radiology team colleagues with appropriate experience in assessing the sacroiliac joints on CT to identify incidental CTSI as per current literature (35).
- In general, contrast-enhanced CTs are performed for the above indications unless there is known contrast allergy or renal impairment. However, differentiation of scans with and without the use of contrast was not specifically recorded as contrast enhancement does not add value to the assessment of bone lesions on CTs (40,41).

6.2 Screening participants

Eligible patients for Phase 1 will be sent a screening questionnaire (which is part of the invitation package). The completed screening questionnaire will be returned via a prepaid return envelope included with the invitation package.

If the patient declines to participate in the study, they are still encouraged to return the screening questionnaire for notification purposes, and a subsequent reminder letter will not be sent.

If the patient meets the eligibility criteria (See Section 5) and has given written consent to be contacted for Phase 2, they will be contacted by the researcher and a clinic appointment at the rheumatology department arranged.

If the patient meets the eligibility criteria (See Section 5), and has declined to be contacted for Phase 2, a letter of appreciation will be sent out to them and their study involvement will end.

If the patient does not meet the eligibility criteria (See Section 5), a letter of appreciation will be sent out to them and their study involvement will end.

During any telephone contact, the screening of eligibility criteria (especially the exclusion criteria) will be checked verbally before an appointment is offered. If any exclusion criteria are present, the patient will not proceed to Phase 2. A letter of appreciation will be sent out to them and their study involvement will end.

6.3 Consenting participants

Every eligible patient will be sent a participant information sheet (PIS). They will be given approximately four weeks to review the information on the PIS (See Appendix C), which will contain the contact information for the study team should they have any queries.

The patient will be given the opportunity to indicate their wish to participate in the study by completing statements in the screening questionnaire (See Appendix F). They will give written consent to be contacted by the research team for Phase 2 of the study. They will also give written consent for access and use of their medical data relevant to the study. They will be considered to be enrolled in Phase 1 of the study by the return of the screening questionnaire.

The participants who meet the eligibility criteria for both Phase 1 and 2 (See Section 5) and have given permission to be contacted for Phase 2, will be contacted by the research team who will arrange a clinic appointment at the rheumatology department.

Formal written consent (See Appendix D) will be obtained at the clinic appointment after further discussion if needed. More time will be allowed if required by the participant to make the decision to take part in Phase 2 of the study. They will also indicate their consent to share their participation and results with their GP (See Appendix E).

7. Statistical Methods

7.1 Power Calculation

There are no reported studies of comparable design. There are no previous reports of the prevalence of rheumatologist verified diagnosed axSpA in a cohort of IBD patients who have incidental CT defined sacroiliitis (suggestive of axSpA) done for non-MSK indications.

Previous studies in the literature have estimated symptomatic CTSI to be between 3% and 45%. We know from our clinical practice that at least 30% of patient with CTSI will have symptoms (clinical experience).

If we assume that 30% of the subjects in the population have symptomatic CTSI and that all will agree to participate in Phase 2 (n = D, See Figure 1 – Study Flow Chart), the number of participants who will have to respond positively to the questionnaire is 21 for estimating the expected proportion with a total width of confidence interval of 42% and 95% confidence level (n = C, See Figure 1 – Study Flow Chart).

If we assume that only 80% will participate in Phase 2 of the study, then the number of participants who will have to responded positively to the questionnaire is 27. Assuming a 50% response rate to questionnaires, a minimum number of 54 subjects will have to be screened for the study (i.e. n = B, See Figure 1 – Study Flow Chart). This is a minimum estimation as we are expecting to identify more patients via our service evaluation.

In summary, using the Binomial "exact" calculation due to likely small sample size:

- Confidence interval = 95%
- Expected population = 30%
- Total width of confidence interval = 42%
- Sample size = 21
- Expected positive results in sample = 6
- Source = http://www.sample-size.net/sample-size-conf-interval-proportion/
- Further assumptions:
    - Sample size = 27 (correcting for those declining to join Phase 2)
    - Sample size = 54 (correcting for those not replying to questionnaire)

7.2 Proposed Analysis and CT Screening Tool Assessment

Descriptive statistics will be used for patient characteristics.

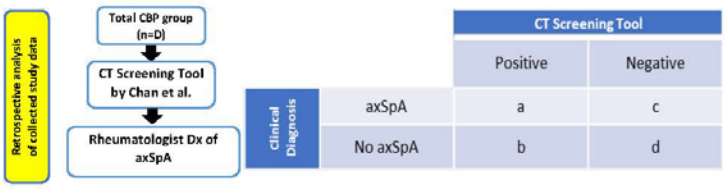
For the calculation of what proportion of IBD patients with incidental CTSI have a rheumatologist verified diagnosis of axSpA, simple proportion of the frequency of those with the diagnosis of axSpA *(n = F)* to the frequency of those subjects who are clinically assessed in phase 2 *(n = E)* will be used; with a calculated confidence interval for the proportion (see Study flow chart, Figure 1). The proportion of patients fulfilling ASAS classification criteria for axSpA will be calculated in an identical manner.

For the calculation of symptomatic vs asymptomatic CTSI in IBD patients with incidental CTSI, this refers to the proportion of those with CBP *(n = D)* relative to all subjects who responded to the screening questionnaire (n = C) vs proportion of those without CBP (n = G) relative to total subjects who responded to the screening questionnaire (n = C), with a calculated confidence interval for the proportion (see Study flow chart, Figure 1).

The utility of the CT Screening Tool (See Appendix Q) in aiding a final diagnosis of axSpA will be measured in terms of sensitivity and specificity. Positive and negative predictive values including likelihood ratios and diagnostics odd ratio will also be determined. This analysis is done retrospectively after the completion of participant involvement. There is no additional intervention or procedures and will not affect the participant's further care. The calculation is shown in Figure 2.

The estimated sensitivity is [a/(a+c)], specificity is [d/(b+d)], positive predictive value is [a/(a+b)], negative predictive value is [c/(c+d)], LR+: positive likelihood ratio is [a/(a+c)]/[b/(b+d)], LR-: negative likelihood ratio is [c/(a+c)]/[d/(b+d)], and diagnostics odd ratio is [LR+/LR-] of the CT screening tool to aid with the identification of axSpA in symptomatic incidental CTSI

Figure 2 – CT Screening Tool Assessment



8. Funding

The study is being funded by AbbVie. The study funding has been reviewed by the NNUH Research Office, and deemed sufficient to cover the requirements of the study.

9. Data Collection and Management

9.1 Data collection, transfer, and recording

Data will be collected by research team, on paper forms which include the Screening Questionnaire (SQ), Case Report Form (CRF), and Rheumatologist Diagnosis Sheet (RDS). These will be supplemented with data from patient medical notes, electronic letters and electronic/paper investigation results to complete any missing data if needed. The data collected will be entered onto an electronic Excel spread sheet. A full list is detailed below.

Screening Questionnaire (See Appendix F)

- Subject's details and consent:
  - Q1: Full name, date of birth, age, address, main contact number, gender
  - Q2: Statement – Decline to join the study
  - Q3: Statement – Consent to be contacted for Phase 2 of study
  - Q4: Statement – Consent to data access and storage
  - Q5: Statement – Involvement of General Practitioner
- Subject's previous diagnosis:
  - Q6: Statement – Previous diagnosis of AS or axSpA, with free text to provide further details
- Main questionnaire:
  - Q7: Question – Back pain last more than 3 months, with diagram to indicate site of pain
  - Q8: Question – Age of onset of back pain
  - Q9: Question – Mode of onset
  - Q10: Question – Radiation of pain to legs
  - Q11: Question – Alternating buttock pain
  - Q12: Question – Night pain
  - Q13: Question – Pattern of back pain/stiffness with time of day
  - Q14: Choice – Time taken for improvement of back pain
  - Q15: Question – Effect of exercise on back pain
  - Q16: Question – Effect of rest on back pain

- Q17: Question – Effect of NSAIDS on back pain
- Q18: Question – Other MSK pain, with diagram to indicate site
- Q19: Choice – Indication of family history of associated axSpA conditions
- Q20: Choice – Previous personal history of associated axSpA conditions

- Brief Inflammatory Bowel Disease (IBD) questionnaire
  - Q21: Choice – type of IBD
  - Q22: Question – Age of symptoms onset and age of diagnosis by gastroenterologist
  - Q23: Question – Duration of IBD diagnosis
  - Q24: Choice – Current treatment for IBD, with area for free text
  - Q25: Choice – Previous surgery or hospitalisation due to IBD
  - Q26: Question – Participant description of current IBD activity
  - Q27: Question – Participant description of gastroenterologist impression of their current IBD activity

Case Report Form (See Appendix G)

- Section 1: Structured History
  - ITEM 1: Demographics and habits
  - ITEM 2: Description of back pain; Judgement on IBP
  - ITEM 3: Back pain pattern graph
  - ITEM 4: Details of axSpA associated conditions
  - ITEM 5: Other past medical history / Co-morbidity
  - ITEM 6: Allergies and current medications (including NSAIDS)
  - ITEM 7: Family History and Social History
  - ITEM 8: Any other relevant symptoms/history/notes
- Section 2: Structured Examination
  - ITEM 9: General Examination & BMI
  - ITEM 10: 44 Swollen / 46 Tender Joint Count
  - ITEM 11: Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
  - ITEM 12: Dactylitis Count
  - ITEM 13: Tender points examination (42)
- Section 3: Rheumatological Outcome Measures

- ITEM 14: BASMI (43), Chest expansion, Occiput-to-wall distance
- ITEM 15: Patient report outcome measures (PROMS) – BASDAI (44), BASFI (45), BASG (46)

- Section 4: Gastroenterology Disease Activity Outcome Measures
  - ITEM 16: Disease Activity for Crohn's Disease – HBI (Harvey-Bradshaw Index) (47–49)
  - ITEM 17: Disease Activity for Ulcerative Disease – PMS (Partial Mayo Score) Disease Activity for Ulcerative Disease – PMS (Partial Mayo Score) (50–53)
- Section 5: Investigation Results
  - ITEM 18: Laboratory Results – HLA-B27, CRP, ESR
  - ITEM 19: Imaging Results – MRI of SIJ and spine, MDT discussion notes
- Section 6: Diagnosis
  - ITEM 20: RVD of axSpA OR Alternative diagnosis
- Section 7: Classification (only when there is a RVD of axSpA)
  - ITEM 21: IBP Classification [Calin (54), Berlin (55), ASAS IBP criteria (56)]
  - ITEM 22: axSpA Classification [ESSG axSpA criteria (57), ASAS axSpA (9) criteria, mNYC AS criteria (58) – the radiographic criterion is based on the radiologists' consensus opinion/grading at a Radiology MDT of the latest available X-ray of the AP pelvis/SIJ or any latest CT imaging of the SIJ based on the modified New York criteria (58) in a retrospective manner only in subjects with a RVD of axSpA]

Rheumatologist Diagnosis Sheet (See Appendix H)

- Is there a diagnosis axSpA before reviewing investigations (YES / NO) and Level of confidence (0 = not confident; 10 = very confident). Offer an alternative diagnosis if there is no diagnosis of axSpA (if possible).
- Is there a diagnosis of axSpA after reviewing investigations (YES / NO) and Level of confidence (0 = not confident; 10 = very confident). Offer an alternative diagnosis if there is no diagnosis of axSpA (if possible).

9.2 Data management

During the study, any paper notes will be stored in study files in a room with restricted access. The data collected on paper (Screening Questionnaire, Case Report Form, etc.) will be transcribed to an Excel spreadsheet on NHS computers and stored on NHS Trust Network Drive with standard NHS information technology security and data management.

Identifiable data (Screening Questionnaire, Consent Forms, paper blood results and imaging results print out) will be stored separately from other study documents in a locked filling

cabinet in a room with restricted access. Participants will be identified by a unique Participant Identification Number (PIN) for all other paper study documents. Only the linking documents (Screening Questionnaire and Consent Forms) will have both identifiable data and PIN. Participants' electronic data will be coded by a unique Data Number. Only an electronic Data Key will link the PIN and Data Number (i.e. electronic database). The electronic Data Key will be stored separately from the electronic database.

Access to collated participant data will be restricted to the Chief Investigator and/or appropriate qualified personnel from the research team. Computers used to collate the data will have limited access measures via user names and passwords. The accumulated electronic data will be analysed in a coded or anonymised manner.

Access to participants' personal/identifiable data may be required by appropriately qualified personnel from the research team (who may be different from those usually involved with the patient's care), sponsor company, the ethics committee and others responsible for overseeing research studies. This information is specified in the Patient Information Sheet, Screening Questionnaire and Patient Consent Form. Patients will give their written informed consent for the above personnel to have access to their data.

The storage and use of data after then end of the study will be describe in Section 16: Study Record Retention / Archiving. This section should also be read with Section 11.2: Good Clinical Practice – Confidentiality and Section 11.3: Data Protection.

10. Risk Assessment and Safety

10.1 Blood test

Blood tests have a wide range of uses and are one of the most common types of medical test. It is likely that a patient with IBD would have prior experience with blood tests. The blood test may cause pain, bruising and rarely a vasovagal reaction. These adverse effects are normally short lived and reversible. Most subjects will normally experience some discomfort but will be accepting of this test.

10.2 MRI Scans

MRI scans are safe and painless, although they can be uncomfortable – especially for some patients, lying still for long periods of time. The MRI scan using the trust's axSpA protocol, will require the participant to be in the scanner for approximately 30mins. This is well within what is considered as a tolerable period even for patients with known diagnosis of ankylosing spondylitis. Many patients will have previously experienced longer scan times, for e.g. whole-spine MRI. Patients may be excluded from the study if they have contraindications to MRI, due to safety concerns – these are as per standard clinical practice and are listed above (See section 5.3 Exclusion criteria). A standard NNUH MRI Patient Information leaflet will be provided to the participant for more information (See Appendix I).

10.3 Incidental findings

Once a radiographer has completed the MRI scan, the images will be reviewed by the local radiologist who will produce a clinical report. We would expect the clinical reports to be sent back to us within 2 weeks.

If the scans (or blood tests) identify something of clinical concern, the participant and their general practitioner will be notified as per usual NHS care (this is highlighted in the Participant Information Sheet and Participant Consent Form).

At the end of the study, the participants that have completed the Phase 2 (Clinical Assessment) will be sent a formal letter. This will include an interpretation of test results and diagnosis including any incidental findings. The letter will also include a recommendation that participants discuss the findings with their GP. It will be stated clearly that the letter will be copied to their GP, so that their GP is aware of their individual outcome of the study. The patient's subsequent care will be directed by the participant's general practitioner. The participant's GP will be responsible for any subsequent follow-up of the incidental findings.

10.4 Adverse Events and Justification of non-reporting

An adverse event is any untoward medical event affecting a clinical trial participant. This is normally included in study protocols such as CTIMPs and observational studies where patients are reviewed sequentially. This study is a prospective, cross-sectional and non-interventional observational study. It is the observation of a symptomatic participant in a point interval in time utilising a single clinical visit with routine investigations as per standard of care (similar assessment would be done if they have been identified later via their general practitioner or specialist doctor). This information and adjunctive information through the postal screening questionnaire will help to decide on the probability of an undiagnosed associated condition in a patient already under routine primary/secondary care review. As such it is not feasible to adopt usual adverse event reporting procedures.

However, if any adverse events do occur within the confines of the study point interval (*this is liken to a routine NHS clinic appointment where clinical assessment is followed by a period of investigation leading to a possible diagnosis or no diagnosis*), and comes to our attention, the researchers will notify the patient's current responsible routine primary and/or secondary care teams to relay the any necessary information as per usual NHS care, so that further appropriate care for the patient can be planned, by their responsible physician.

Adverse events

The investigators agree with the Sponsor that non-serious adverse events will not be reported to the Trust R&D department because there is no intervention in this study. However, non-serious adverse events will be recorded by the researchers and must continue to be reported into the Trust's clinical risk systems, for example, adverse events which may occur during the normal routine procedures for the patient pathway i.e. during blood draw, x-ray and MRI.

Expected serious adverse events

The investigators agree with the Sponsor that this study is a prospective, cross-sectional and non-interventional observational study, where the focus of the study is to help to decide on the

probability of detecting an undiagnosed associated condition in a patient already under routine primary/secondary care review. It is expected that this patient population may require hospitalisation, experience new medical problems and deterioration of existing medical problems. In recognition of this, events fulfilling the definition of a serious adverse event will not be reportable in this study. These events will be recorded by the researchers, but will not be subject to expedited reporting to the Research Ethics Committee (REC) but will be reported annually to the REC (in the annual progress report).

Additional Statement from Funders

Safety Signal: Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the adverse reaction.

Sponsor must report to AbbVie any potential new safety signal in their data collection which may have potentially causal association or a new aspect of a known association with AbbVie product and therefore justifies further analysis, within 15 calendar days of identification.

All safety data: Serious AEs, non-serious AEs, product complaint, all special situations including pregnancy

If safety data is collected by Sponsor, summarize in the final report. Timeline for provision of final report to Abbvie to align with study end as specified in contract.

The Sponsor will do the above with cooperation from the Chief Investigators and/or Principle Investigators.

10.5 New diagnosis

Distress may be caused by receiving a letter in the post suggesting that their IBD diagnosis could be linked to another condition. The results of the assessment/scan could be distressing for some patients, if diagnosed with a new chronic condition. However, patients who are diagnosed with IBD are routinely given information from the charity CORE (59) by the gastroenterology team about their condition and they will be aware that inflammation in the gut may also trigger inflammation outside the intestine leading to arthritis, eye inflammatory or skin complaints (See Appendix J).

They should be relieved when they attend the rheumatology appointment as this would provide an opportunity for any concerns or queries to be addressed while being assessed and investigated by a specialist. The distress should be balanced against the benefits of an earlier diagnosis and potential treatment of their symptoms. This is highlighted in the Participant Information Sheet.

11. Good Clinical Practice

11.1 Ethical Conduct of the Study

The study will be conducted in accordance with the principles of good clinical practice.

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

11.2 Confidentiality

We will obtain study information from consented study participants. However, we will not undertake any of these activities during the identification of potential participants. The radiology team (this is the direct healthcare team) will have a list of patients identified for recruitment with personal identifiable data. These patients will then be sent an invitation package to their home address. The returned Screening Questionnaire will contain personal identifiable information. Patients will return their questionnaire to the rheumatology department, providing consent for the research team to make contact with them. The patient is then enrolled as a participant and a unique Participant Identification Number (PIN) will be issued. The signed Consent Form at the clinical assessment visit will also contain patient identifiable information with the linking PIN.

From this point onwards, all further data collecting physical forms (e.g. Case Report Form, Rheumatologist Diagnosis Sheet, etc.) will use the PIN instead of personal identifiable data. A Data Key will be used to convert the PIN to a Data Number. All electronic data will be coded using the Data Number instead of the PIN. The data collected on paper (Screening Questionnaire, Case Report Form, etc.) will be transcribed to an Excel spreadsheet. Further to this, the accumulated electronic data will be analysed in a coded or anonymised manner.

The researchers are contractually bound by their terms of employment to ensure that personal data remains confidential, in adherence with the NHS Code of Confidentiality. Identifiable data will only be held on patients who have given consent as this is a condition of entry into the trial. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

11.3 Data protection

The CI and study staff involved with this study will comply with the requirements of the General Data Protection Regulation and Data Protection Act 2018 for health and care research, with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to the CI and appropriate study staff. Computers used to collate the data will have limited access

measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

12. Trial Management & Governance

12.1 General Management and Roles

The trial will be overseen by the Chief Investigator / Principle Investigator who will be responsible for the day-to-day management of the trial. He/she will co-ordinate all routine study procedures – in particular (a) ensuring that all ethics and research governance approvals are adhered to; and (b) training of investigators; and (c) responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the CI or delegated member of the study team. If the CI is not available the Co-Principle Investigator will take on the role of "acting CI".

The Principle Investigators will ultimately be responsible for the relevant clinical care of the participants for the duration of their participation. A study-specific delegation log (See Appendix K) will be prepared detailing the responsibilities of each member of staff working on the study.

12.2 Governance and Monitoring

The CI and PIs will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation. Monitors will be given access to the CRFs and database (on a read only) basis.

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

13. Training

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate curriculum vitae and training records (e.g. GCP training, See Training Log – Appendix O) will be maintained in the study files.

14. Insurance and Indemnity

Norfolk & Norwich University Hospital NHS Foundation Trust (NNUH) is the lead sponsor of the study. The University of East Anglia (UEA) is the co-sponsor. The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research. The University of East Anglia (UEA) hold insurance on the academic aspects of the study.

15. Protocol Amendments and Deviations

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study documents will not be implemented without these approvals.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be confirmed by the Sponsor. Both substantial and minor amendments will follow the submission and approval process outlined on the HRA website (https://www.hra.nhs.uk/approvals-amendments/amending-approval/). All amendments will be submitted to the research office(s) for approval before they are implemented. All staff working on the study will be updated of the approved amended documents and previous versions will be kept and marked as 'superseded' for reference.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

16. Study Record Retention / Archiving

The investigators agree to archive and/or arrange for secure storage of study materials in accordance with NNUH UEA SOP 900 – Storage and Retention of Research Documents. Documents/Data will be kept for a minimum of 5 years after the end of the study, including the identity of all participating patients (sufficient information to link records, Screening Questionnaire and original signed Participant Consent Form), to enable evaluations and/or audits from regulatory authorities.

Any paper data will be stored in a secured location with restricted access as determined by the Sponsor or, representatives of the Sponsor. Electronic data will be kept on the Sponsor's electronic data network with standard NHS information technology security. Access will be restricted to the Data Custodian or another appropriate person as determined by the Sponsor or, representatives of the Sponsor. Computers for access of the data will have limited access measures via user names and passwords.

Final study data set without any identifiable data or PIN or Data Number may be shared with the wider research community for ethically approved future studies when deemed appropriate by the Data Custodian or another appropriate person as determined by the Sponsor or, representatives of the Sponsor. This should be done in consultation with the Sponsor or, representatives of the Sponsor and should always conform to contemporary legal, ethical and regulatory framework including appropriate acknowledgement.

17. End of study

The participant's involvement in the study ends when they receive a final letter communicating the diagnosis and all relevant investigation results to patient (and GP) as describe in Section 4: Study Design. The patient's subsequent care will be directed by the participant's general practitioner. For patients who did not go through the clinical assessment, their active participation will end when they receive the letter of appreciation for completing the screening questionnaire.

The end of recruitment (date of last invitation package being sent out) is at the end of the 1st month post start of study (date of completion of an appropriately completed screening questionnaire received by the research team). The last MRI scan is estimated to be at the end of the 4th month post start of study. The last letter of appreciation or final communication letter

is estimated to be sent (at the latest) 5th month post start of study. The end of study is defined as 10 months after the start of study.

The Sponsor and CI have the right at any time to terminate the study for clinical or administrative reasons.

The CI shall notify the REC and the Sponsor in writing within 90 days of the study conclusion, or of the early termination of a study, using the NRES Declaration of the End of Trial Form available from the HRA website (http://www.hra.nhs.uk). The CI will ensure that any appropriate follow up is arranged for all participants.

The CI shall work with the Sponsor to prepare and submit to the REC and Sponsor a summary of the study within 12 months of the end of the study.

18. Publication and Dissemination

Authorship policy

Ownership of the data arising from this study resides with the CI and his/her respective employer. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, shall belong to the CI and his/her respective employer.

Publication

The clinical study report will be used for publication and presentation at scientific meetings. The CI will have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to stakeholders for dissemination (where appropriate and according to their discretion).

Publication plan

The intention is to publish in a specialist rheumatology journal. An initial abstract of the study with initial data will be available approximately from the 9th month post start of study. The final abstract and journal submission will full data will follow approximately from 10th month post start of study depending on data analysis and administrative processes. This is only a tentative timeline outline which may be subjected to changes depending on the study's progress.

Recognition and Acknowledgement

All publications, communications, presentations, posters and broadcasts (or any other material) relating to the study will acknowledge the funders support.

Peer review

- The project has been reviewed by the AbbVie Investigator-Initiated Study Programme Review Panel during the funding application process before funding is awarded.

- The project has also been peer-reviewed internally by the Rheumatology Department, Radiology Department (Professor Andoni Toms), Research Team, Clinical/Educational Supervisor (Professor Karl Gaffney) and Academic/Educational Supervisor (Professor Alexander MacGregor).

Reporting

Reports will be produced for Sponsor, REC and R&D as agreed in contracts and approval letters.

19. References

1. Hamilton L, Barkham N, Bhalla A, Brittain R, Cook D, Jones G, et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology. 2017 Feb 1;56(2):313–6.

2. Keat A, Bennett AN, Gaffney K, Marzo-Ortega H, Sengupta R, Everiss T. Should axial spondyloarthritis without radiographic changes be treated with anti-TNF agents? Rheumatol Int. 2017 Mar;37(3):327–36.

3. Sieper J, Rudwaleit M, Khan MA, Braun J. Concepts and epidemiology of spondyloarthritis. Best Pract Res Clin Rheumatol. 2006 Jun;20(3):401–17.

4. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol. 2012 May;8(5):262–8.

5. Slobodin G, Eshed I. Non-Radiographic Axial Spondyloarthritis. Isr Med Assoc J IMAJ. 2015 Dec;17(12):770–6.

6. Lambert RGW, Bakker PAC, van der Heijde D, Weber U, Rudwaleit M, Hermann KG, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann Rheum Dis. 2016 Nov;75(11):1958–63.

7. Rudwaleit M, Jurik AG, Hermann K-GA, Landewé R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis. 2009 Oct;68(10):1520–7.

8. Rudwaleit M, Landewé R, Heijde D van der, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009 Jun 1;68(6):770–6.

9. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009 Jun;68(6):777–83.

10. Zink A, Listing J, Klindworth C, Zeidler H. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. Ann Rheum Dis. 2001 Mar;60(3):199–206.

11. Seo MR, Baek HL, Yoon HH, Ryu HJ, Choi H-J, Baek HJ, et al. Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis. Clin Rheumatol. 2015 Aug;34(8):1397–405.

12. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009 Mar;60(3):717–27.

13. Sieper J, Heijde D van der, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013 Jun 1;72(6):815–22.

14. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatol Oxf Engl. 2015 Dec;54(12):2283–4.

15. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis. 2017 May 1;11(5):631–42.

16. de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis Res Ther. 2016 01;18:196.

17. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis. 2015 Jan;74(1):65–73.

18. Salvarani C, Fries W. Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease. World J Gastroenterol. 2009 May 28;15(20):2449–55.

19. Brown MA, Kenna T, Wordsworth BP. Genetics of ankylosing spondylitis--insights into pathogenesis. Nat Rev Rheumatol. 2016 Feb;12(2):81–91.

20. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol. 2006 Jun;20(3):451–71.

21. Braun J, Baraliakos X, Regel A, Kiltz U. Assessment of spinal pain. Best Pract Res Clin Rheumatol. 2014 Dec 1;28(6):875–87.

22. Sieper J. How to screen for axial spondyloarthritis in primary care? Curr Opin Rheumatol. 2012;24(4):359.

23. Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. Ann Rheum Dis. 2005 May;64(5):659–63.

24. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis. 2015 Nov;74(11):1990–5.

25. Sykes MP, Hamilton L, Jones C, Gaffney K. Prevalence of axial spondyloarthritis in patients with acute anterior uveitis: a cross-sectional study utilising MRI. RMD Open. 2018 Feb 1;4(1):e000553.

26. Bruining DH, Siddiki HA, Fletcher JG, Tremaine WJ, Sandborn WJ, Loftus EV. Prevalence of penetrating disease and extraintestinal manifestations of Crohn's disease detected with CT enterography. Inflamm Bowel Dis. 2008 Dec;14(12):1701–6.

27. Paparo F, Bacigalupo L, Garello I, Biscaldi E, Cimmino MA, Marinaro E, et al. Crohn's disease: prevalence of intestinal and extraintestinal manifestations detected by computed tomography enterography with water enema. Abdom Imaging. 2012 Jun;37(3):326–37.

28. Gotler J, Amitai MM, Lidar M, Aharoni D, Flusser G, Eshed I. Utilizing MR enterography for detection of sacroiliitis in patients with inflammatory bowel disease. J Magn Reson Imaging JMRI. 2015 Jul;42(1):121–7.

29. Chan J, Sari I, Salonen D, Silverberg MS, Haroon N, Inman RD. Prevalence of Sacroiliitis in Inflammatory Bowel Disease Using a Standardized CT Scoring System. Arthritis Care Res. 2017 Jul 21;

30. Eno J-JT, Boone CR, Bellino MJ, Bishop JA. The prevalence of sacroiliac joint degeneration in asymptomatic adults. J Bone Joint Surg Am. 2015 Jun 3;97(11):932–6.

31. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int. 2003 Mar;23(2):61–6.

32. Pialat J-B, Di Marco L, Feydy A, Peyron C, Porta B, Himpens P-H, et al. Sacroiliac joints imaging in axial spondyloarthritis. Diagn Interv Imaging. 2016 Aug;97(7–8):697–708.

33. Geijer M, Gadeholt Göthlin G, Göthlin JH. Diagnosis and progression of sacroiliitis in repeated sacroiliac joint computed tomography. Arthritis. 2013;2013:659487.

34. Prakash D, Prabhu SM, Irodi A. Seronegative spondyloarthropathy-related sacroiliitis: CT, MRI features and differentials. Indian J Radiol Imaging. 2014 Jul;24(3):271–8.

35. Chan J, Sari I, Salonen D, Inman RD, Haroon N. Development of a Screening Tool for the Identification of Sacroiliitis in Computed Tomography Scans of the Abdomen. J Rheumatol. 2016;9.

36. Forster D, Warburton L, O'Flynn N. Diagnosis and management of spondyloarthritis in the over-16s: NICE guideline. Br J Gen Pract J R Coll Gen Pract. 2018 Jul;68(672):346–7.

37. Hamilton L, Macgregor A, Newman D, Belkhiri A, Toms A, Gaffney K. Validation of a patient self-reported screening questionnaire for axial spondyloarthropathy in a UK Population. Spine. 2013 Mar 15;38(6):502–6.

38. Hermann K-GA, Baraliakos X, van der Heijde DMFM, Jurik A-G, Landewé R, Marzo-Ortega H, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. Ann Rheum Dis. 2012 Aug;71(8):1278–88.

39. Braun J, Sieper J. Ankylosing spondylitis. Lancet Lond Engl. 2007 Apr 21;369(9570):1379–90.

40. Woertler K. Benign bone tumors and tumor-like lesions: value of cross-sectional imaging. Eur Radiol. 2003 Aug;13(8):1820–35.

41. Miwa S, Otsuka T. Practical use of imaging technique for management of bone and soft tissue tumors. J Orthop Sci. 2017 May 1;22(3):391–400.

42. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990 Feb;33(2):160–72.

43. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 1994 Sep;21(9):1694–8.

44. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994 Dec;21(12):2286–91.

45. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994 Dec;21(12):2281–5.

46. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 1996 Jan;35(1):66–71.

47. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet Lond Engl. 1980 Mar 8;1(8167):514.

48. Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology. 2002 Feb;122(2):512–30.

49. Info HBI | Harvey-bradshaw index [Internet]. [cited 2018 Jul 15]. Available from: https://www.igibdscores.it/en/info-hbi.html

50. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987 Dec 24;317(26):1625–9.

51. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462–76.

52. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the Non-invasive Components of the Mayo Score to Assess Clinical Response in Ulcerative Colitis. Inflamm Bowel Dis. 2008 Dec;14(12):1660–6.

53. Info MAYO | Partial [Internet]. [cited 2018 Jul 15]. Available from: https://www.igibdscores.it/en/info-mayo-partial.html

54. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA. 1977 Jun 13;237(24):2613–4.

55. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum. 2006 Feb;54(2):569–78.

56. Sieper J, van der Heijde D, Landewé R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis. 2009 Jun;68(6):784–8.

57. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991 Oct;34(10):1218–27.

58. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984 Apr;27(4):361–8.

59. Patient Information Leaflets – Core [Internet]. [cited 2017 Aug 1]. Available from: http://corecharity.org.uk/resources-for-patients/patient-information-leaflets/

20. Appendices

A Invitation Letter – See separate document from protocol
B Letter of Appreciation – See separate document from protocol
C Participant Information Sheet – See separate document from protocol
D Participant Consent Form – See separate document from protocol
E GP Information Sheet – See separate document from protocol
F Screening Questionnaire – See separate document from protocol
G Case Report Form
H Rheumatologist Diagnosis Sheet
I NNUH Magnetic Resonance Imaging (MRI) Patient Information
J IBD patient information by charity CORE
K Delegation Log
L BASDAI Form
M BASFI Form
N BASG Form
O Training Log
P General study letter template
Q CT SCREENING TOOL

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

University of East Anglia

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Direct dial: 01603 286154
Direct fax: 01603 286146
Switchboard: 01603 286286

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label

Dear Sir/Madam,

Re: Recruitment To The N-ASPIRE CT Strategy Study

We are undertaking a research project, with our colleagues in the rheumatology department, in patients who had Computer Tomography Scan (CT Scans) of their abdomen and/or pelvis done in the past for their inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis). They are particularly interested in people who have also suffered from back pain, either recently, or for a significant amount of time in the past. This could be a symptom of arthritis related to your inflammatory bowel disease.

Please find enclosed more information about the study. If you have any questions please contact the rheumatology department using the details in the PIS (Participant Information Sheet).

We would be grateful if you could complete the enclosed questionnaire and return it in the stamped addressed envelope.

Yours sincerely

Verified Electronically

Radiology Department

Encs
- Participant Information Sheet
- Screening Questionnaire

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Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

University of East Anglia

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LETTER OF APPRECIATION

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label

What proportion of patients with Inflammatory Bowel Disease have Axial Spondyloarthritis – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis [Norfolk - Axial SPa Ibd REferral Computer Tomographic Strategy (N-ASPIRE CT Strategy)]

Dear Sir/Madam,

Thank you for your completing the questionnaire for the above study.

On review of the questionnaire, you did NOT fulfil the eligibility criteria OR decline to be contacted for the next phase of the study. As such, your participation will now end.

We value your time and effort in the participation of the study. Thank you.

If you have any questions please contact the Rheumatology Research Team.

Yours sincerely,

Dr Chong Seng Edwin Lim
Senior Research Fellow (Rheumatology)

Professor Karl Gaffney
Rheumatology Consultant

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PARTICIPANT INFORMATION SHEET

We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Feel free to contact us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. *See the Flow Chart for an overview on page 5.*

Study Title

What proportion of patients with Inflammatory Bowel Disease have Axial Spondyloarthritis – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis [Norfolk - Axial SPa Ibd REferral Computed Tomography Strategy (N-ASPIRE CT Strategy)]

Study Title Explanation

How common is axial spondyloarthritis (axSpA, an inflammatory back disease) picked up in patients with inflammatory bowel disease (IBD) such as Crohn's Disease (CD) and Ulcerative Colitis (UC) who have undergone Computed Tomography (CT) scans for their bowel symptoms?

What is the purpose of the study?

IBD can sometimes be associated with an arthritis called axial spondyloarthritis (axSpA). The arthritis causes inflammation in the spine resulting in back pain, stiffness or reduced range of movement of the spine.

This condition is often diagnosed late because back pain is common and this condition is a relatively uncommon cause of back pain. It is important to make this diagnosis as early as possible in order to receive the most effective treatment.

The aim of the study is to find out the following:

1. The number of people with IBD (who have changes on a previous imaging done for the assessment their bowel disease) who have an additional diagnosis of axSpA.
2. The results will also help to assess the usefulness of a screening tool that may help to guide further management of IBD patients. This will reduce the time to diagnosis and enable the earlier access to available treatments.

Why have I been invited?

You previously had a CT Scan of the abdomen and/or pelvis at the Radiology Department at the Norfolk and Norwich University Hospital (NNUH) for your IBD (CD or UC). This may be a considerable time ago. Patients who have changes of their sacroiliac joints (a joint between the spine and the pelvis) on the scan will be invited to take part in this study.

We would like to invite people who have had back pain at any point in the past, or who have ongoing back pain. However, even if you have never had back pain, we would be grateful if you could still return the attached

questionnaire as the information can still be helpful to us. In addition, it will inform us of your wishes so that you are not disturbed with a 2nd invitation letter.

Do I have to take part?

The decision to participate depends on the individual. If you do decide to take part, then you should keep this information sheet and you will be asked to sign a consent form at a later stage.

If you would prefer not to take part in the study, we would still be grateful if you could return the enclosed questionnaire, ticking the "I would prefer not to take part in the study" box so that we do not send you a second invitation letter. Please note that a decision not to take part will not affect the standard of care you would otherwise receive within the NHS.

What will happen to me if I take part?

If you agree to take part, firstly you would need to complete the questionnaire enclosed with this letter and return it in the stamped envelope. See Flow Chart for an overview on page 5.

1. If the information provided on the questionnaire does NOT suggest that you could have the condition, your participation will end.
2. If the information provided on the questionnaire suggests that you could have the condition, you will be invited to attend a clinic appointment organised by the rheumatology department.

At this appointment:

- A rheumatologist specialist doctor will explore your symptoms and medical history. There will be a physical examination and measurements of your spinal movements. The appointment will take about one hour.
- You will then have blood taken (single sample for three bottles; which will be discarded after analysis) for adjunctive diagnosis markers – CRP (C-reactive protein); ESR (Erythrocyte Sedimentation Rate); HLA-B27 (Human Leucocyte Antigen B27). The procedure will take about 10 minutes.

Following the appointment, a Magnetic Resonance Imaging (MRI) scan in the radiology department will be organised for you at a second visit to the hospital. The scan will last around 30 minutes and will look at your mid-to-lower back and pelvis. You will find a NNUH patient information leaflet on MRI scanning enclosed.

Your travel expenses for attending the study visits will be reimbursed (maximum of £10 pounds per participant per visit).

We will inform you and your General Practitioner (GP) of the diagnosis including any unexpected test results if present. Your participation in this study will end at that point. Any further care you may require will be arranged through your GP.

During the analysis part of the study, we will review your final diagnosis against a set of known definitions regarding changes at your sacroiliac joint seen on your previous CT Scan. This is done to determine if these set of definitions (CT Screening Tool) will be useful to identify future patients with axSpA.

What are the possible benefits of taking part?

You will have an opportunity to find an explanation for your back pain. If you are found to have inflammation in your spine or other potentially treatable causes of back pain, we will recommend that your GP refer you to the rheumatology clinic and you may be given some different treatment to help manage your symptoms.

What are the possible disadvantage and risks of taking part?

We may be able to diagnose you with having axSpA which may have implications for your day-to-day life (as being diagnosed with any chronic disease would) but we hope that the opportunity to start treatment is likely to outweigh any distress of this findings.

There are some risks and discomfort associated with the routine procedures which are undertaken to diagnose axSpA, these are:

- Blood collection: For most people, needle punctures for blood withdrawal do not cause any bad problems. However, sometimes they may cause bleeding, bruising, discomfort, infections, and/or pain where the skin is punctured. You may also feel dizzy.
- MRI: The risk associated with having an MRI of the spine and pelvis is very minimal. However, if you are claustrophobic (have a fear of closed spaces) or have had any metal placed in your body (for example, during a surgery), **you should let us know if we contact you to arrange a clinic appointment.** See attached NNUH MRI Patient Information leaflet for more information.

By taking part in this study we will not expose you to any risks which would be outside of your usual care. As with any test, we would like to make you aware that there is a possibility that the results of the above investigations may identify another cause for your symptoms that may be unrelated to the study. This information will be forwarded to you and your general practitioner who will decide on your further care.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time without giving a reason if you wish and this will not affect your standard of care. If you do withdraw from the study, we will destroy all of your identifiable personal data, but unless you specifically ask otherwise, we will retain and use any anonymised research data collected as part of the study, up to that point.

Will my taking part in this study be kept confidential?

Yes. All study materials will identify you using only a unique identification number. Your name and contact details will be stored separately from all other study materials and all data storage (both paper and electronic) will be kept secure at all times – only study personnel who need to will have access to your data. Electronic data will be kept securely on Trust computers with password-protected access and we will comply with all Data Protection legislation.

If you consent to take part in the research, relevant parts of your medical records and information collected may be inspected by the institution/company funding or sponsoring the research for purposes of analysing/verifying the results and safety/regulatory investigation. They may also be looked at by people from the institution/company, regulatory authorities and hospital trust to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

We would routinely inform your GP that you have agreed to take part in the study and we would also inform your GP of the results of the study. In Phase 1 (Questionnaire) of the study you can choose to opt out of this process.

Your personal data and research data will be kept for a minimum of 5 years after the end of the study according to the Trust's policy.

What will happen to the results of the study?

You will be contacted by letter with your individual results and a copy of this letter will also be sent to your GP.

The final study report will be published in a medical journal or at a medical conference. The final report will NOT include any personal details, and NO individual participants will be identified.

We will ask your permission for your anonymised data (this is data that will NOT include any personal details, and NO individual participants will be identified) to be shared with the wider research community for ethically approved future studies.

Who is organising and funding the research?

The research is being organised by the Rheumatology Department of Norfolk and Norwich University Hospital NHS Foundation Trust in collaboration with the University of East Anglia (UEA). The funding for the study has been provided by the pharmaceutical company AbbVie. The company will not have access to any of your personal identifiable data.

Who has reviewed the study?

All Research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the East of England - Essex Research Ethics Committee.

What if something goes wrong?

Independent advice is available from the Patient Advocacy and Liaison Service (PALS) and the Independent Complaints Advisory Service (ICAS).

PALS: PALS Office, Level 2 West Outpatient, Norfolk and Norwich University Hospital
01603 289045

ICAS: 01273 229 002

Contacts for further information

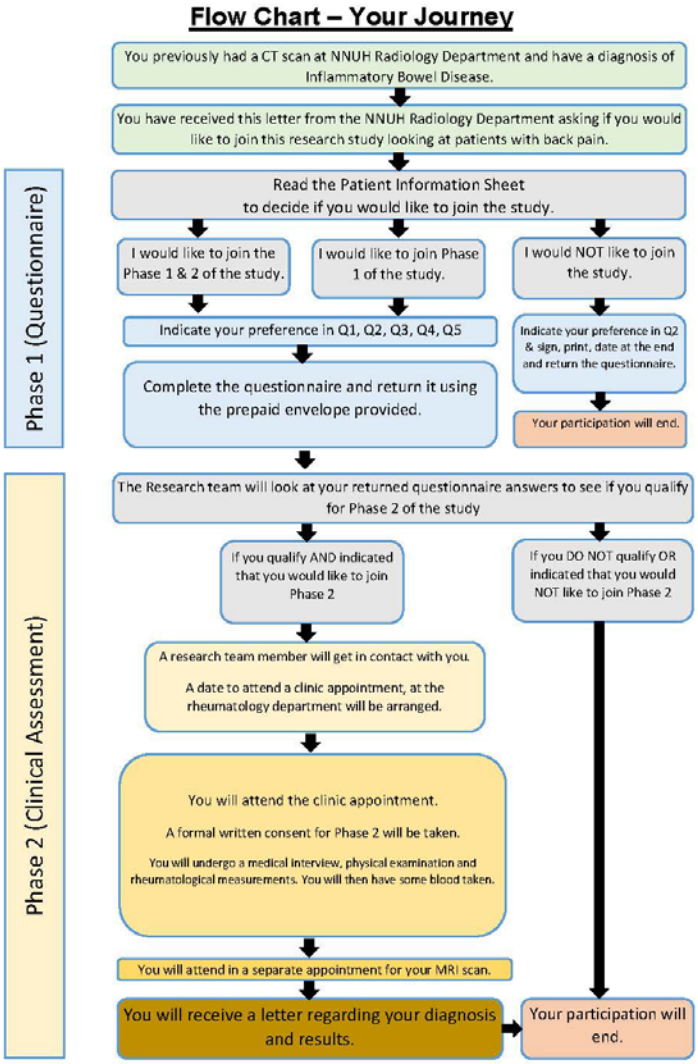
If you require any additional information, please do not hesitate to contact either Dr Edwin Lim or Prof Karl Gaffney.

Rheumatology Department
Norfolk and Norwich University Hospital NHS Foundation Trust,
Colney Lane, Norwich NR4 7UY
01603 647835 or 01603 287119

What happens next?

If you would like to take part in the study, please complete the enclosed questionnaires and return it in the envelope provided.

Thank you for considering taking part in this study


Flow Chart – Your Journey
You previously had a CT scan at NNUH Radiology Department and have a diagnosis of Inflammatory Bowel Disease.
You have received this letter from the NNUH Radiology Department asking if you would like to join this research study looking at patients with back pain.
Phase 1 (Questionnaire)
Read the Patient Information Sheet to decide if you would like to join the study.
I would like to join the Phase 1 & 2 of the study.
I would like to join Phase 1 of the study.
I would NOT like to join the study.
Indicate your preference in Q1, Q2, Q3, Q4, Q5
Complete the questionnaire and return it using the prepaid envelope provided.
Indicate your preference in Q2 & sign, print, date at the end and return the questionnaire.
Your participation will end.
Phase 2 (Clinical Assessment)
The Research team will look at your returned questionnaire answers to see if you qualify for Phase 2 of the study
If you qualify AND indicated that you would like to join Phase 2
If you DO NOT qualify OR indicated that you would NOT like to join Phase 2
A research team member will get in contact with you.
A date to attend a clinic appointment, at the rheumatology department will be arranged.
You will attend the clinic appointment.
A formal written consent for Phase 2 will be taken.
You will undergo a medical interview, physical examination and rheumatological measurements. You will then have some blood taken.
You will attend in a separate appointment for your MRI scan.
You will receive a letter regarding your diagnosis and results.
Your participation will end.

Additional information on

PATIENT INFORMATION AND HEALTH AND CARE RESEARCH

All NHS organisations (including Health & Social Care in Northern Ireland) are expected to participate and support health and care research. The Health Research Authority and government departments in Northern Ireland, Scotland and Wales set standards for NHS organisations to make sure they protect your privacy and comply with the law when they are involved in research. Our research ethics committees (https://www.hra.nhs.uk/about-us/what-we-do/how-we-regulate-health-and-social-care-research/) review research studies to make sure that the research uses of data about you are in the public interest, and meet ethical standards.

Health and care research may be exploring prevention, diagnosis or treatment of disease, which includes health and social factors in any disease area. Research may be sponsored by companies developing new medicines or medical devices, NHS organisations, universities or medical research charities. The research sponsor decides what information will be collected for the study and how it will be used.

Health and care research should serve the public interest, which means that research sponsors have to demonstrate that their research serves the interests of society as a whole. They do this by following the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/). They also have to have a legal basis for any use of personally-identifiable information.

How patient information may be used for research

When you agree to take part in a research study, the sponsor will collect the minimum personally-identifiable information needed for the purposes of the research project. Information about you will be used in the ways needed to conduct and analyse the research study. NHS organisations may keep a copy of the information collected about you. Depending on the needs of the study, the information that is passed to the research sponsor may include personal data that could identify you. You can find out more about the use of patient information for the study you are taking part in from the research team or the study sponsor. You can find out who the study sponsor is from the information you were given when you agreed to take part in the study.

For some research studies, you may be asked to provide information about your health to the research team, for example in a questionnaire. Sometimes information about you will be collected for research at the same time as for your clinical care, for example when a blood test is taken. In other cases, information may be copied from your health records. Information from your health records may be linked to information from other places such as central NHS records, or information about you collected by other organisations. You will be told about this when you agree to take part in the study.

Keeping information for future research

Information about you that is collected during a research study may be kept securely to be used in future research in any disease area, including research looking at social and economic factors affecting health. This may include combining it with information about you held by other health or government organisations such as NHS Digital (https://digital.nhs.uk/about-nhs-digital/our-work/keeping-patient-data-safe/how-we-look-after-your-health-and-care-information). Usually the information is combined together by matching information that has the same NHS number (https://digital.nhs.uk/services/nhs-number). Doing this makes maximum use of the information you have provided and allows researchers to discover more.

Researchers may not be able to specify all the possible future uses of the information they keep. It could include providing the information to other researchers from NHS organisations, universities or companies developing new treatments or care. Wherever this happens it will be done under strict legal agreements. The information about you will be depersonalised wherever possible so that you cannot be identified. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

On rare occasions NHS organisations may provide researchers with confidential patient information from your health records when we are not able to seek your agreement to take part in the study, for example because the

number of patients involved is too large or the NHS organisation no longer has your contact details. Researchers must have special approval before they can do this.

Your choices about health and care research

If you are asked about taking part in research, usually someone in the care team looking after you will contact you. People in your care team may look at your health records to check whether you are suitable to take part in a research study, before asking you whether you are interested or sending you a letter on behalf of the researcher.

In some hospitals and GP practices, you may have the opportunity to sign up to a register to hear about suitable research studies that you could take part in. If you agree to this, then research nurses, researchers or administrative staff authorised by the organisation may look at your health records to see if you are suitable for any research studies.

It's important for you to be aware that if you are taking part in research, or information about you is used for research, your rights to access, change or move information about you are limited. This is because researchers need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from a study, the sponsor will keep the information about you that it has already obtained. They may also keep information from research indefinitely.

If you would like to find out more about why and how patient data is used in research, please visit the Understanding Patient Data website.

https://understandingpatientdata.org.uk/what-you-need-know

Further information is available, depending on where in the UK you live:

England

In England you can register your choice to opt out via the NHS website (http://www.nhs.uk/my-data-choice). If you do choose to opt out you can still agree to take part in any research study you want to, without affecting your ability to opt out of other research. You can also change your choice about opting out at any time.

Northern Ireland

If you would like to find out more about how and why your information is used, including for research purposes, please visit the Department of Health website (https://www.health-ni.gov.uk/articles/privacy-notice-doh).

Scotland

Members of the public in Scotland have their rights and responsibilities set out in the Patients' Rights (Scotland) Act 2011. For information on confidentiality of data (including in research) please visit the NHS Inform website (https://www.nhsinform.scot/care-support-and-rights/health-rights/confidentiality/confidentiality-when-using-the-nhs).

Wales

If you would like to find out more about how and why your information is used, including for research purposes, please visit NHS Direct Wales (http://www.nhsdirect.wales.nhs.uk/lifestylewellbeing/yourinfoyourrights).

What to do if there is a problem

If you wish to raise a complaint on how any research organisation has handled your personal data, you can contact the relevant Data Protection Officer who will investigate the matter. If you are not satisfied with their response or believe they are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO) (https://ico.org.uk/).

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Switchboard: 01603 286286

PARTICIPANT CONSENT FORM

Study Title: What proportion of patients with Inflammatory Bowel Disease have Axial Spondyloarthritis – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis [Norfolk - Axial SPa Ibd REferral Computed Tomography Strategy (N-ASPIRE CT Strategy)]

Investigators: Dr Chong Seng Edwin Lim
Prof Karl Gaffney

Patient Full Name:	
Personal Identification Number (PIN)	

	Please read the following statements and put your initials in the box to show that you have read and understood them and that you agree with them.	**Please initial each box**
1	I confirm that I have read and understand the information sheet Version ____ dated _____ for the above study. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.	
2	I understand that my involvement is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	
3	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals (Research Team, Sponsors, Regulatory Authorities, NHS Trust) where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4	I agree to the processing of my data as described and further explained in the Patient Information Sheet.	
5	I agree to my GP being informed of my participation in the study and the results of any investigations including unexpected findings or an adverse event.	

ONE copy for patient, ONE copy for medical notes, ORIGINAL to be file in Study File

Optional Statements		
Please read the following statements and put your initials in the box to show that you have read and understood them and that you agree to opt in.		
6	I agree to be contacted by the study team for ethically approved future studies that they may be undertaking. I understand that identifiable contact information will be kept after the end of this study and this information will be held in accordance with data protection legislation.	
7	I agree for anonymised data to be shared with the wider research community for ethically approved future studies.	

To be completed by the patient **I freely agree to take part in the above study**		
Your name	Date (Day/Month/Year)	Signature

To be filled in by the person obtaining consent (investigator) **I confirm that I have explained the nature, purposes and possible risk and benefit the research study to the person whose name is printed above. They agreed to take part by signing and dating above.**		
Your name	Date (Day/Month/Year)	Signature

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CONSULTANTS
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Colney Lane
Norwich
NR4 7UY

Direct dial 1: 01603 287621
Direct dial 2: 01603 647835
Switchboard: 01603 286286

GP Information Sheet

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label

What proportion of patients with Inflammatory Bowel Disease have Axial Spondyloarthritis – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis [Norfolk - Axial SPa Ibd REferral Computed Tomography Strategy (N-ASPIRE CT Strategy)]

The above named patient is known to have a previous CT abdomen and/or pelvis scan (with changes at the sacroiliac joints) done at the radiology department at the Norfolk and Norwich University Hospital with a known diagnosis of Inflammatory Bowel Disease (IBD).

As IBD is often associated with axial spondyloarthritis (axSpA), this study has been proposed to investigate the hidden prevalence of axSpA in this group of patients.

This man/women has been contacted and has agreed to take part in the study.

Last paragraph will be added depending on scenario (Delete as necessary):

- **We will assess the patient in the rheumatology department and inform you of the results afterwards.** *(Screen positive and agree for contact in Phase 2)*
- **The patient has completed a screening questionnaire but has not agreed to join the clinical phase of the study. Their participation has ended.** *(Screen positive but decline for participation in Phase 2)*
- **The patient has completed a screening questionnaire but is not eligible for the clinical phase of the study. Their participation has ended.** *(Screen negative regardless of interest to participation in Phase 2)*

Yours sincerely,

Dr Chong Seng Edwin Lim
Senior Research Fellow (Rheumatology)
Professor Karl Gaffney
Rheumatology Consultant

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SCREENING QUESTIONNAIRE

- ***For Q1 to Q5 – Please select those options that apply to you.***
- ***For the rest of the questionnaire, please kindly fill in ALL the BLANKS and mark the boxes ☐ with a CROSS ☒ if applicable as you go through the questionnaire sequentially.***

Subject's details and consent

Q1 About yourself (all information will be strictly confidential)

Full Name:				
Date of Birth:			Age:	
Address:				
Main contact number:				
Gender:	Male ☐	Female ☐	Prefer not to say ☐	

Q2 I have read the attached Participant Information Sheet (Version ____ dated _____) and I would prefer **NOT** to take part. ☐

! If you have indicated that you prefer NOT to take part in the study, there is NO need to complete the rest of the questionnaire. Please sign and date the form at the end. Kindly return it to us in the prepaid envelope. Thank you.

Q3 I have read the attached Participant Information Sheet (Version ____ dated _____) :- (**Choose ONE option below**)

- *I am happy to complete this questionnaire **AND** to be contacted for an appointment to attend the rheumatology department for clinical assessment (Phase 2 of study).* ☐
- *I am happy to complete this questionnaire **BUT** I prefer **NOT** to take part in the clinical assessment (Phase 2 of study).* ☐

Q4 Data Access and Storage:- (**Select ALL that apply**)

- *I give permission for the researchers to access and use all my relevant medical information for the purpose of this study.* ☐
- *I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals (Research Team, Sponsors, Regulatory Authorities, NHS Trust) where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.* ☐
- *I agree to be contacted by the study team for future studies. I understand that identifiable contact information will be kept after the end of this study and this information will be held in accordance with data protection legislation.* ☐
- *I agree for my data to be shared with the wider research community for future studies if I cannot be identified in the data.* ☐
- *I agree to the processing of my data as described and further explained in the Patient Information Sheet.* ☐

Q5 Involvement of your General Practioner (GP):- (**Choose ONE option below**)

- *I AGREE to my GP being informed of my participation in the questionnaire.* ☐
- *I would prefer that my GP was NOT informed of my participation in the questionnaire.* ☐

Subject's previous diagnosis

Q6 I already have a diagnosis of:

Anklyosing Spondylitis ☐
Axial sponlyloarthritis/sponlyloarthropathy ☐
If yes, please provide further details in the box below (e.g. who made the diagnosis, whether you attend hospital outpatients appointments, when it was diagnosed).

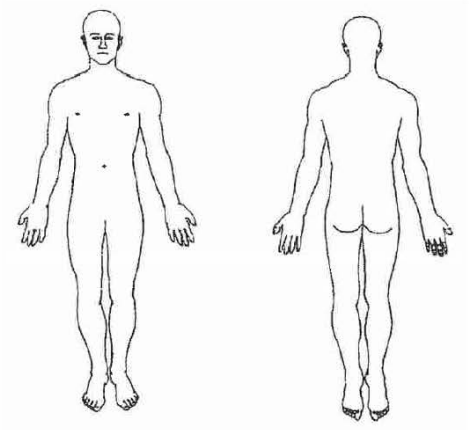
We will review your medical records and if we are able to verify this then you do not need to continue with the Phase 2 of the study. Thank you.

Main questionnaire

Q7 Have you had back pain or stiffness lasting for at least 3 months?

YES ☐
NO ☐

If yes, please mark the site of pain on the diagram



Q8 How old were you when the pain started?

- Less than 18 years old ☐
- 18 – 25 years old ☐
- 26 – 33 years old ☐
- 34 – 40 years old ☐
- 41 – 44 years old ☐
- more than 44 years old ☐

Q9 Did the pain or stiffness start:

- Gradually ☐
- Suddenly (e.g. after falling / lifting / twisting) ☐

Q10 Have you had pain or numbness spreading down your legs?

- YES ☐
- NO ☐

Q11 Have you had buttock pain which moves from side to side?

- YES ☐
- NO ☐

Q12 Are you woken up by back pain or stiffness?

- First half of the night ☐
- Second half of the night ☐
- Throughout the night ☐
- Not woken up ☐

Q13 What happens to your pain/stiffness as the day goes on?

- Gets better ☐
- Gets worse ☐
- No change ☐

Q14 If it gets better, how long does this take:

- Within 15 mins ☐
- Within 30 mins ☐
- Within 60 mins ☐
- Within 2 hours ☐
- More than 2 hours ☐

Q15 What effect does exercise have on your back pain and stiffness?

Increases pain/stiffness	☐
Decrease pain/stiffness	☐
No effect on pain/stiffness	☐

Q16 What effect does resting have on your back pain or stiffness?

Increases pain/stiffness	☐
Decrease pain/stiffness	☐
No effect on pain/stiffness	☐

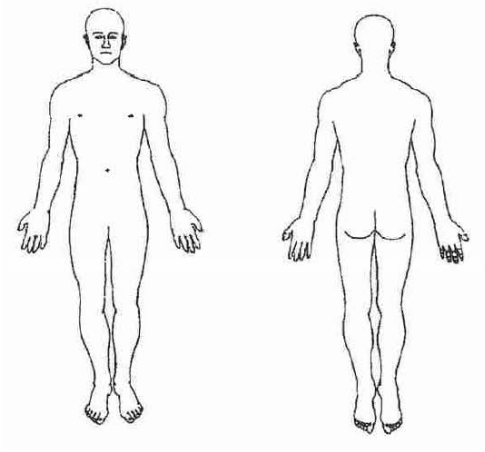
Q17 What effect do anti-inflammatory drugs (e.g. ibuprofen, diclofenac, naproxen) have on your back pain?

Increases pain/stiffness	☐
Decrease pain/stiffness	☐
No effect on pain/stiffness	☐
I havent taken anti-inflammatories	☐

Q18 Have you had pain in any other places e.g. joints, heels?

YES	☐
NO	☐

If YES, please mark on diagram (below):



Q19 Do any close relative (parents, children, brothers or sisters) have:

- Anklyosing Spondylitis or Axial sponlyloarthritis/sponlyloarthropathy ☐
- Anterior Uveitis / Iritis ☐
- Psoriasis ☐
- Inflammatory Bowel Disease ☐
- Reactive Arthritis ☐

Q20 Have you ever been diagnosed with any of the following conditions

- Reactive Arthritis ☐
- Achillies Enthesopathy or Plantar fasciitis ☐
- Dactylitis ☐
- Psorasis ☐
- Anterior Uveitis / Iritis ☐

Brief Inflammatory Bowel Disease (IBD) questionnaire

Q21 Please indicate the type of IBD you are diagnoses with?

- Crohn's Disease ☐
- Ulcerative Colitis ☐

Q22 What was the age when your IBD symptoms started and diagnosed by your gastroenterologist?

Age symtpoms started (give an estimate rounded number): ☐

Age diagnosis made by gastroenterologist (give an estimate rounded number): ☐

Q23 How long have you been diagnosed with IBD?

Duration of your IBD diagnosis since diagnosis: ☐
(Give an estimate rounded number in **months** e.g. 1 yr + 1 mth = 13 months)

Q24 Please indicate the types of treatment you are **currently** on for the treatment or manaintence of your IBD (select as many as needed)?

- *Rectal topical steriods* e.g. hydrocortisone, etc ☐
- *Rectal aminosalicylate* (5-ASA) medications e.g. mesalazine, etc ☐
- *Oral steriods* e.g. budesonide, prednisolone, beclometasone, etc ☐
- *Oral aminosalicylate (5-ASA) medications* e.g. mesalazine, olsalazine, sulfasalazine, etc ☐
- *Immunomodulator therapy* e.g. azathioprine, mercaptopurine, methotraxate, etc ☐
- *Biological therapy* e.g. infliximab, adalimumab, vedolizumab, ustekinumab, etc ☐
- *None*. I am not on any treatment. ☐
- *Others*. Not stated in the groups above. Please describe in the box below: ☐

Q25 Please indicate if you had the following due to your Inflammatory Bowel Disease?

- Previous surgery for your Inflammatory Bowel Disease? ☐
- Hospitalisation due to your Inflammatory Bowel Disease? ☐

Q26 How would you describe your current Inflammatory Bowel Disease activity?

- Remission (NOT active) ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Unsure ☐

Q27 Do you know what your gastroenterologist think about your current IBD activity?

- Remission (NOT active) ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Unsure ☐

This questionnaire will be returned to the rheumatology research team who are conducting the trial and any further correspondence regarding the study will be with this team.

Thank you. You have come to the end of the questionnaire. Please return it in the prepaid envelope.

Signature:	
Print Name:	
Today's Date:	

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CASE REPORT FORM

PIN _____

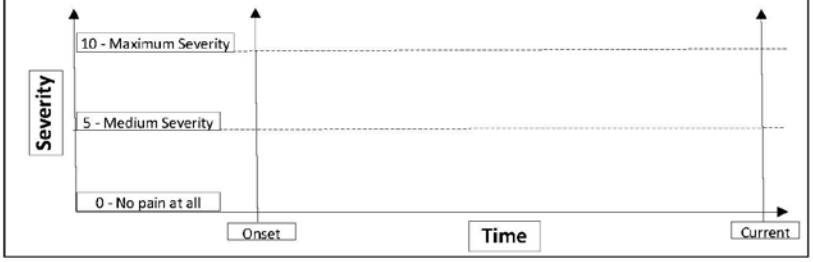
DATE SEEN: _____

Section 1: Structured History

ITEM 1	Demographics & Habits
Gender:	
Age:	
Alcohol:	current intake in units/week
Smoking:	never/ex/current smoker & pack years

ITEM 2	Description of back pain
Age of 1st onset of back pain	
Site of back pain?	cervical / thoracic / lumbar / mixed / not around spine
Radiation to legs?	yes / no
Alternating buttock pain?	yes / no
Gradually onset?	yes / no
Duration of back pain ≥ 3mth	yes / no
When is the back pain/stiffness worse?	morning / afternoon / evening / whole day
Are you woken by back pain/stiffness?	1st ½ of night / 2nd ½ of night / whole night / Not woken up
What happens to your pain/stiffness as the day goes on?	better / worse / no change
If it gets better, how long does this take?	15 / 30 / 60 / 120 / >120min
What effect does exercise have on your back pain and stiffness?	increase / decrease / none
What effect dose resting have on your back pain or stiffness?	increase / decrease / none
What effect do anti-inflammatory drugs have on your back pain?	increase / decrease / none / not taken anti-inflammatories
Do you think there is IBP (inflammatory back pain)	yes / no
Description & Comments (free text):	

ITEM 3	Back Pain Pattern Graph



PIN _____

ITEM 4	Details of axSpA associated conditions
Previous/Current diagnosis of arthritis, enthesitis or dactylitis	yes / no ; A / E / D
Previous/Current diagnosis of other muculoskeletal problems?	yes / no
Muculoskeletal problem details: (Diagnosis, number, location, treatment)	
Previous/Current diagnosis of anterior uveitis?	yes / no
Previous/Current diagnosis of eye problems?	yes / no
Eye problem details: (Diagnosis, number of episodes, treatment received within past year)	
Previous/Current diagnosis of psoriasis?	yes / no
Previous/Current diagnosis of skin problems?	yes / no
Skin problem details: (Diagnosis, current status, treatment received within past year)	
Previous/Current diagnosis of IBD?	yes / no
Type (CD or UC)?	CD / UC
Age of symptom onset (estimation in years)?	
Age of diagnosis (estimation in years)?	
Duration of disease since diagnosis (estimation in months)?	
Did you receive treatment for your IBD previously?	yes / no
Are you current on treatment for your IBD?	yes / no
Are you currently on steriods?	yes / no
Are you on biological therapy?	yes / no
Previous operations for IBD?	yes / no
Previous hospitalisation for IBD?	yes / no
How do you rate your current IBD activity?	remission / mild / moderate / severe / unsure
Do you know your gastroenteriologist's impression of your current IBD activity?	remission / mild / moderate / severe / unsure
IBD and Treatment details: (Previous & Current Treatment details; either from patient or medical records or re-verified with gastroenteriologist. [1] basis of IBD diagnosis [2] extend or classification of disease [3] current disease activity) Recorded last current IBD activity by Gastroenterologist (e.g HBI/partial Mayo index/Others if present) - Not active (remission); Active (mild/moderate/severe); Unclear; Not recorded	
ITEM 5	Other past medical history / Co-morbidity

PIN _____

ITEM 6	Allergies and current medications		
Do you use NSAIDS for your musculoskeletal symptoms?			yes / no
Type	Dose	Frequency	Effect on pain/stiffness
			increase / decrease / none
Others medications & analgesia:			

ITEM 7	Family History and Social History
Do any close relative (parents, children, brothers or sisters) have Anklyosing Spondylitis or Axial sponlyloarthritis/sponlyloarthropathy; Psoriasis; Anterior Uveitis; Reactive Arthritis; Inflammatory Bowel Disease?	yes / no
Details / Any other significant family history?	
Occupation / Others?	

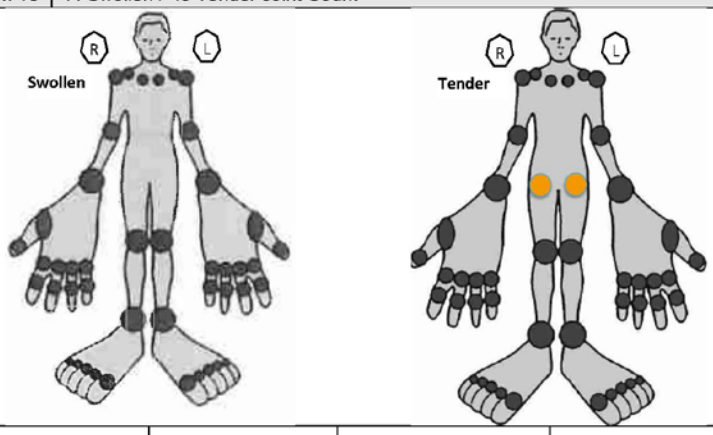
ITEM 8	Any other relevant symptoms/history/notes

Section 2: Structured Examination

ITEM 9	General Examination
• Weight, Height, BMI • Skin = check for psoriasis espically elbows, nails, umbilicus, natal clef or flexure of breast • GALS screen • Eyes, CVS, Resp, Abdo, Neuro	

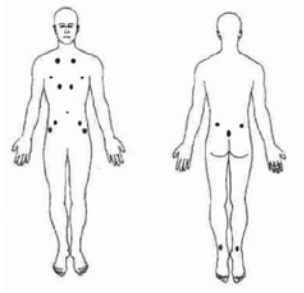
PIN _____

ITEM 10	44 Swollen / 46 Tender Joint Count



Swollen Joints	/44	Tender Joints	/46

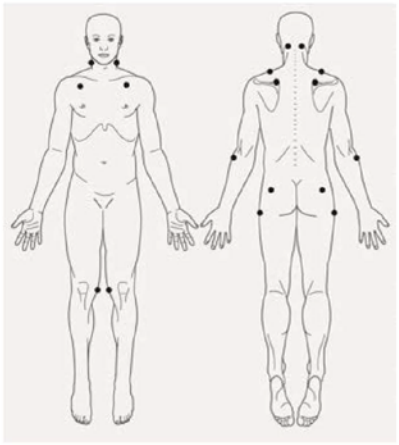
ITEM 11	Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)



Site	R	L
1st Costochondral		
7th Costochondral		
Anterior superior iliac spine		
Iliac Crest		
Posterior superiour iliac spine		
L5 spinous process		
Proximal achilles tendon insertion		
MASES	/13	

ITEM 12	Dactylitis Count
Number of digits with clinical dactylitis	/20
Details: (name the digit, record tenderness yes/no)	

PIN _____

ITEM 13	Tender points examination (ACR 1990 Fibromyalgia Classfication Criteria)		
	Site	R	L
	Suboccipital		
	Lower cervical (laterall by the C5-C6 tranverse processes)		
	At the midpoint of the upper Trapezius border		
	Suprapinatus by its orgin medially in the supraspinatus fossa		
	Intercoastal space above the 2nd rib and just lateral to the costochrondral junction		
	2cm distal to the lateral epicodyle		
	In the centre of the upper lateral quadrant of the gluteal region		
	Greater tronchanter		
	Medially on the medial femur condyle, just proximal to the joint line		
	Total number of tender point that are positive	/18	
	Evidence of widespread pain (4 quardants of the body) for > 3 months	yes / no	
	Clinical impression of fibromyalgia	yes / no	

PIN _____

Section 3: Rheumatological Outcome Measures

ITEM 14	BASMI & Other Measurements															
Category	Measurements															
Chest expansion (x2 difference reading, level of the 4th intercoastal level, higher of the two reading recorded)	1st		2nd		Best											
Occiput-to-wall distance (x2 readings, lower of the two readings recorded)	1st		2nd		Best											
Category	BASMI Measurements															Score
Tragus-to-wall distance (x2 readings, lower of the two readings recorded, REPEAT, mean of the lower reading of each side recorded)	R1		R2		Best		L1		L2		Best		Mean			
Cervical rotation (x2 readings, higher of the two readings recorded, REPEAT, mean of the higher reading of each side recorded)	R1		R2		Best		L1		L2		Best		Mean			
Lateral spinal flexion (x2 readings, higher of the two readings recorded, REPEAT, mean of the higher reading of each side recorded)	R1		R2		Best		L1		L2		Best		Mean			
Lumbar flexion (Modified Schobers) (x2 difference reading, level of the lumbosacral junction, higher of the two reading recorded	1st		2nd		Best											
Intermalleolar distance (x2 readings, higher of the two readings recorded)	1st		2nd		Best											
															BASMI =	
ITEM 15	Patient report outcome measures (PROMS)															
BASDAI		Notes:														
BASFI																
BASG																

PIN _____

Section 4: Gastroenterology Disease Activity (Depends on Type of IBD)

ITEM 16	Disease Activity for Crohn's Disease – HBI (Harvey-Bradshaw Index)	
No.	Details	Score
A	General wellbeing (0=very well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)	
B	Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)	
C	Number of liquid stools per day	
D	Abdominal mass (0=none, 1=dubious, 2=definite, 3=definite and tender	
E	Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item).	
	TOTAL Score =	
	Score Definition =	
Calculation: • Calculation formula: sum of the scores of all 5 parameters. • A score below 5 is generally considered as clinical remission. A reduction of 3 points is considered as relevant to define clinical response. Scoring definition: • Remission < 5; Mild Disease 5-7; Moderate Disease 8-16; Severe Disease >16		
Source: • Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet Lond Engl. 1980 Mar 8;1(8167):514. • Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002; 122: 512-530. • Info HBI | Harvey-bradshaw index [Internet]. [cited 2018 Feb 28]. Available from: http://www.igibdscores.it/en/info-hbi.html		

ITEM 17	Disease Activity for Ulcerative Disease – PMS (Partial Mayo Score)	
No.	Details	Score
1	Stool Frequency (per day) [0=normal number of stool, 1=1-2 more than normal, 2=3-4 more than normal, 3=≥5 more than normal]	
2	Rectal Bleeding (indicate the most severe bleeding of the day) [0=none, 1=streaks of blood with stool in less than half of the cases, 2=obvious blood with stools in most cases, 3=blood alone passes]	
3	Physician's global assessment [0=normal, 1=mild disease, 2=moderate disease, 3=severe disease]	
	TOTAL Score =	
	Score Definition =	
Calculation: • Calculation formula: sum of the scores the three parameters. Scoring definition: • Remission < 2; Mild Disease 2-4; Moderate Disease 5-7; Severe Disease >7		
Source: • Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Eng J Med 1987; 317 (26): 1625-1629. • Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005; 353 (23): 2462-2476. • Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008; 14 (12): 1660-1666. • Info MAYO | Partial [Internet]. [cited 2018 Feb 28]. Available from: http://www.igibdscores.it/en/info-mayo-partial.html		

PIN _____

Section 5: Investigation Results

ITEM 18	Laboratory Results	
HLA B27	positive / negative	
CRP	mg/L	
ESR	mm/hr	
ITEM 19	Imaging Results	
MRI of Sacroiliac Joints & Spine		
Radiology MDT discussion notes (if imaging have been discussed)		

Section 6: Diagnosis

ITEM 20	RVD of axSpA OR Alternative diagnosis

Section 7: Classification

ITEM 21	IBP Classification		ITEM 22	axSpA Classification	
Meet Calin IBP Criteria		yes / no	Meets mNYC AS criteria		yes / no
Meet Berlin IBP Criteria		yes / no	Meets ESSG axSpA criteria		yes / no
Meet ASAS IBP Criteria		yes / no	Meets ASAS axSpA criteria		yes / no
Notes:					

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RHEUMATOLOGIST DIAGNOSIS SHEET

Rheumatologist initials: _____

PIN	Dx of axSpA before reviewing Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible	Dx of axSpA after reviewing Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible

Rheumatologist initials: _____

PIN	Dx of axSpA before reviewing Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible	Dx of axSpA after reviewing Ix (YES / NO)	Level of confidence (0 = not confident; 10 = very confident)	Offer an alternative Dx, if possible

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DEPARTMENT OF RADIOLOGY

Magnetic Resonance Imaging (MRI)

What is an MRI scan?
MRI (Magnetic Resonance Imaging) creates high resolution images of the body on a computer using a powerful magnet and radio frequency waves. MRI is a very safe way of producing images that can diagnose medical conditions. Unlike CT (Computed Tomography) it does not use X-rays and has not been shown to have any harmful side effects.

What does it involve?
The MRI scanner is a long open ended tube, surrounded by a large magnet present in the circular area. You will be asked to lie on a scanning table, which will be moved slowly so the part of your body being scanned is in the centre of the scanner. It is important that you remain as still as possible, so that we can get the best images. You will be positioned either head first or feet first depending on the area to be scanned. You will be given ear protection because the scanner makes a loud drumming noise. During the scan, the radiographer will be able to see you from the control room, and hear you via a two-way intercom.
Sometimes an injection will be required to give clearer pictures of certain tissues or organs being examined, but this will be discussed with you if it is necessary.

Will I feel anything?
MRI is entirely painless. You should not feel any discomfort during the scan and experience no after effects.

How long will the scan take?
The length of the scan depends upon the part of the body being imaged and the information your doctor needs. The scanning time can range from 10 minutes being the shortest scan time to 2 hours in length. Although we try our best to keep to appointment times, there can sometimes be unexpected delays.

How do I prepare for my scan?
Most MRI scans need no special preparation. You should continue with any medication. Instructions will be detailed in your appointment letter if necessary. You may eat and drink normally after the procedure.

What happens when I arrive?

You may be asked to change into a gown. Storage may be provided for valuables, but it is advisable to leave them at home. You will not be permitted to take them into the scan room with you.

Prior to your appointment, you will be sent an MRI Safety Questionnaire to complete. This will be checked by the radiographer before your scan to ensure you are safe to have the procedure.

Safety Precautions:

It may not be possible for certain patients to have this examination due to the strong magnetic field produced by the MRI scanner. This can be dependent on implants within your body or operations you have had.

Please contact the MRI department if you have any doubts about your suitability for an MRI scan.

You will need to remove the following before your appointment:

- Jewellery
- Body piercings

Can pregnant women have MR scans?

There have been no reported effects from MRI to the unborn child. We advise against scanning in the first trimester as a precaution. In certain critical cases, it may be necessary to be scanned during pregnancy when a more invasive diagnostic test would otherwise have to be performed.

Results of the scan:

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The results of your MRI scan will be sent to the referring doctor who will arrange a follow up appointment.

If you have any questions regarding the scan please contact the MRI appointments office:

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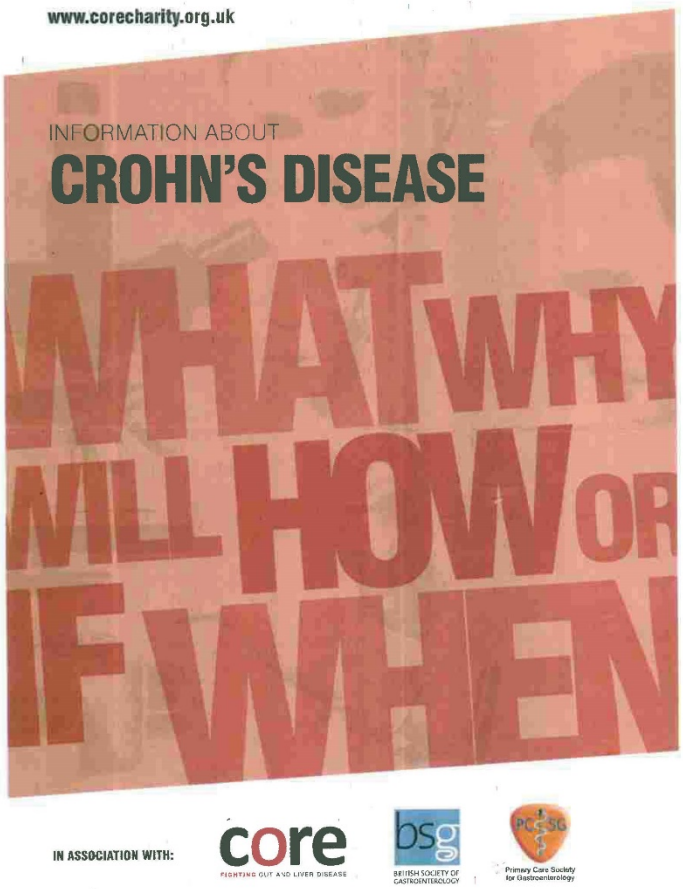
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CROHN'S DISEASE

Crohn's Disease is an illness in which inflammation develops in parts of the gut leading to symptoms such as diarrhoea, abdominal pain and tiredness.

The inflammation can be mild in many cases but can sometimes be severe requiring strong medication or an operation to remove an affected part of the intestine. Crohn's Disease is one of the two conditions known as Inflammatory Bowel Diseases (IBD); with the other being ulcerative colitis. The symptoms and effects are similar to those of gastroenteritis (food poisoning) but differ in that they are not due to an infection and persist for a long time or until treated.

WHO GETS CROHN'S DISEASE?

The disease affects mainly young adults but can affect teenagers or younger children and can sometimes start later in life. Men and women are affected equally. Crohn's Disease affects about 1 in 1000 people (most people know one person affected by the condition). Crohn's Disease and ulcerative colitis can run in families – about one-fifth of people with the condition will have another family member affected[1].

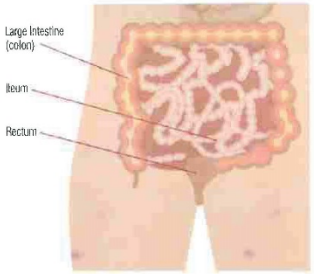
WHAT CAUSES IT?

It is thought that Crohn's Disease develops as a result of the immune system in the intestine reacting abnormally to bacteria at the surface of the gut. This abnormal immune reaction is likely to be inherited with a number of genes that may contribute to causing Crohn's Disease having now been identified, which are mostly involved in how we handle bacteria in the gut[2].

It is still not known if one, a few or many types of bacteria are involved. Other factors affect the chances of getting Crohn's Disease, with smoking being the most important risk factor[3]. Many patients ask whether there is a dietary cause but there is no firm evidence of this[4].

WHICH PART OF THE BODY DOES CROHN'S DISEASE AFFECT?

Any part of the gut can be affected in Crohn's Disease. The most common area is the last part of the small intestine (terminal ileum) and the first part of the large intestine (or 'colon'), near the appendix[5]. In some people, only the colon is affected, in a pattern similar to ulcerative colitis. In others, multiple parts of the gut are affected. Rarely, the mouth, gullet or stomach may be involved. However, in some people, the inflammation in the gut also triggers inflammation outside the intestine leading to arthritis, eye inflammation or skin complaints.



HOW DOES CROHN'S AFFECT THE INTESTINE?

One form of Crohn's Disease results in patches of inflammation in the lining of the intestine with groups of small ulcers, similar to mouth ulcers. In moderate or severe Crohn's Disease, these ulcers become much larger and deeper with a lot of surrounding redness. The inflammation can make the intestine become thickened, blocking the passage of digested food. In some cases, deep ulcers break through the wall of the intestine causing infection outside the bowel (an abscess) and this can then spread to the skin or a nearby part of the body. This is known as a fistula. These most frequently occur around the anus. As the inflammation heals, scar tissue may form which can in some cases also lead to a blockage in the intestine.

WHAT ARE THE SYMPTOMS?

The main symptoms of Crohn's Disease are diarrhoea and abdominal pain. There may be some blood or mucus in the faeces, especially when the lowest part of the gut is affected. Digested food or faeces building up in narrowed or inflamed areas often occurring an hour or so after eating usually cause the pain. Sometimes, there is a tight blockage in the intestine causing severe, griping abdominal pain after eating, with swelling of the abdomen and vomiting. Losing weight is common when there is a lot of inflammation, as eating causes pain and many people with the condition feel excessively tired. Some people also have a temperature or sweats at night. There may also be sore, red eyes, swollen painful joints and skin rashes[5]. Some patients get perianal Crohn's disease which means that the inflammation occurs around the lower bowel and anus.

HOW IS IT DIAGNOSED?

When someone visits their doctor with symptoms of persistent diarrhoea and abdominal pain, they will try to decide whether special tests are needed to look for the possibility of Crohn's Disease and ulcerative colitis. There are many causes of diarrhoea in young adults including the irritable bowel syndrome (IBS), and infection (for example after travel abroad). The doctor will listen to the symptoms and ask about any of the related symptoms described above and also whether there is anyone in the family with Crohn's Disease or ulcerative colitis.

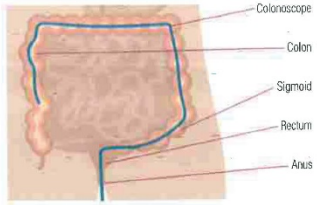
An examination will then find out if there are any signs of inflammation (such as tenderness in the abdomen or a lump) and whether there are any general signs of illness such as looking pale or underweight. A blood test might be arranged to see if there are changes in the blood, which suggest inflammation[6]. If the doctor suspects that Crohn's Disease is a possibility, a referral will be made to a specialist for further tests.

WHICH TESTS ARE USED TO DIAGNOSE CROHN'S DISEASE?

The most frequent test used to diagnose Crohn's Disease is a colonoscopy. This involves the passage of a tube with a video camera at the end around the colon and, where possible, into the last part of the small intestine. Laxative preparation is needed before the examination to clear the bowel and allow good views of the lining of the intestine[6]. In most cases, sedation is given through a vein at the start of the procedure to minimise some feelings of discomfort associated with passage of the tube along the colon.

By doing this test, doctors can get very accurate pictures of the state of the lining of the intestine and take samples for examination in the laboratory. If the colon and last part of the small intestine are seen to be normal, Crohn's Disease is very unlikely to be present.

In some cases, other tests are also needed. For example, a barium follow through examination allows the whole of the small intestine to be shown. In this test, liquid barium is swallowed and X Rays are taken as it passes through the intestine. Increasingly, other methods are used; these include magnetic resonance imaging (MRI) or capsule endoscopy, where a radiopill is swallowed and transmits pictures as it passes through the intestine. Scans such as ultrasound or CT scanning may be needed, especially if an abscess or problems on the outside of the intestine are suspected.



HOW IS CROHN'S DISEASE TREATED?

Treatments for Crohn's Disease aim to reduce or heal the inflammation in the intestine and to deal with the effects of the disease, such as weight loss, and any complications. The inflammation is generally treated with medicines but in some cases surgery is required to cut out very inflamed or narrowed sections of intestine.

Many patients ask whether they should change their diet, but there is no proven specific diet for Crohn's Disease. There are, however, diets for certain situations. The most frequent dietary change is a reduction in fibre and indigestible foods, which cause pain when there is a narrowing in the intestine (a 'low residue diet'). Specialised liquid formula diets ('elemental' or 'polymeric' diets) are also used as treatment in Crohn's Disease, especially when it affects the small intestine. These diets rest the bowel, improve nourishment and reduce inflammation and are used especially in children where maintaining growth and weight is very important.

Medicines used to treat Crohn's Disease are mainly directed at the immune system in the intestine.

- Antibiotics (such as metronidazole) can be helpful, either by reducing the bacteria, which 'drive' the inflammation, or to treat abscesses. They are not used for long-term treatment.
- Aminosalicylates are a relative of aspirin and are used to treat milder inflammation or reduce the chances of recurrence (for example, after an operation). Not all patients are helped by these drugs.
- Steroids (prednisolone, hydrocortisone) are much stronger drugs used to suppress inflammation when the symptoms are more severe. Steroids are very effective (about eight out of ten patients have a good response) but have side effects such as weight gain, insomnia, infection and acne and prolonged use can result in thinning of the bones. Steroids are therefore only used as a short-term measure to get Crohn's Disease under control.[7] There is a newer form of steroid (budesonide) which has fewer side effects due to mostly acting within the gut itself.
- For long term steroid use, immunosuppressive drugs are often used to reduce inflammation over a longer period and allow steroids to be stopped. Azathioprine and 6-mercaptopurine are the most frequently prescribed and around two-thirds of patients have a successful response. Side effects can occur and patients on these drugs therefore need to have regular blood tests. On the whole, however, most patients tolerate the drugs well and they remain the most effective medicine for keeping Crohn's Disease under control.
- Methotrexate is another immunosuppressive drug, commonly used for treating rheumatoid arthritis. This is usually the next choice if azathioprine or 6-mercaptopurine have failed.

The strongest drug treatment used for Crohn's Disease involves 'biological therapy' in which specially developed antibodies are used to block the effects of the molecules that are involved in the inflammation in the gut wall. The best-known biological therapies target a substance called tumour necrosis factor (TNF)[8] and are given by a regular intravenous drip or an injection under the skin. Other similar treatments, which target different inflammatory mediators, are under development. These treatments are very effective but can also have side effects, especially increased rates of infection and allergic reactions, so they are reserved for people with severe Crohn's Disease and when other medicines have not worked. They need to be used under care of hospital specialists.

Surgical operations are a very important part of the treatment of Crohn's Disease and it is estimated that as many as eight out of ten patients will require an operation at some stage in their life. The main reason for needing surgery is to remove thickened blocked segments of the intestine. Medicines are unlikely to help these and an operation to cut out a short section of affected intestine is usually very successful with few problems and restores full health quickly[9]. Sometimes, colonoscopy can be used to open up narrowed sections (with special dilating balloons) but this is only possible in certain cases. Surgery is also needed when badly affected parts of the intestine have caused an abscess or fistula. Such fisula can occur on the abdomen or in the perianal area. An operation can sometimes be the best option when severe Crohn's Disease is not responding to drug treatment.

DOES SURGERY MEAN HAVING A STOMA BAG?

Many people presume that surgery for Crohn's Disease means having a permanent stoma bag. In fact, stomas (ileostomy or colostomy) are not often needed and are nearly always a temporary measure[9]. After a section of affected intestine has been removed, a very delicate join (or 'anastomosis') is made between the unaffected ends of the intestine. In order to protect this join while it heals, the surgeon will often make a temporary stoma above, which is then taken away at a second smaller operation a few months later. This is done particularly when someone is underweight or taking steroids which reduce the ability of body tissues to heal.

DOES CROHN'S DISEASE COME BACK AFTER SURGERY?

Yes as there is no cure for Crohn's Disease so it does come back, often in the section of intestine just above a surgical join. However, despite this, most people have no problems for many years after their operation. Recurrence is two-times more likely in smokers compared those who do not smoke[10]. Drugs such as aminosalicylates or azathioprine can also reduce the chances of recurrence.

DOES CROHN'S DISEASE AFFECT MY CHANCES OF HAVING CHILDREN?

Overall, Crohn's Disease does not have a significant effect on the chances of becoming pregnant or carrying a baby[11]. In a small number of cases, inflammation or infection in the pelvis, or surgery to this area, can affect the ovaries, fallopian tubes or uterus reducing fertility. The commonly used drugs used in Crohn's Disease are safe during pregnancy. It is always best to talk to your specialist if you have Crohn's Disease and are planning a pregnancy or already pregnant.

CAN I EXPECT A NORMAL LIFE IF I HAVE CROHN'S DISEASE?

In most cases, Crohn's Disease does not have much impact on daily life, the ability to work or to enjoy an active social life, but does take some getting used to. When it is active, symptoms such as diarrhoea and abdominal pain often require time away from work, college etc and make it difficult to cope at home or go out. However, treatment usually makes the symptoms better within days or weeks so work and home life is restored quite quickly.

The chances of dying if you have Crohn's Disease are no different to if you don't have the disease[12]. There are many forums and support groups around for those who suffer from Crohn's Disease to join, help and find out more information from. One example is www.crohnsforum.com/

WHAT CAN BE DONE TO PREVENT CROHN'S DISEASE?

There is currently no evidence any particular change in diet or lifestyle can prevent Crohn's Disease. Not smoking, or stopping smoking, is perhaps the most important of all the things to do. Although not proven, it makes sense to eat a balanced healthy diet favouring freshly cooked food over processed foods.

WHAT RESEARCH IS NEEDED?

The cause of Crohn's Disease remains unknown. However, our understanding of how and why the condition develops is increasing all the time. In particular, researchers are looking into how the hereditary (genetic) aspects of Crohn's Disease might change the way the immune system in the intestine deals with bacteria and other dietary substances present at the surface of the gut. This is very important research and there is hope that it will, before too long, lead to much better treatments and maybe even a cure.

REFERENCES:

1. Molodecky Na, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142:46. e42–54.e42, quiz e30.
2. ghr.nlm.nih.gov/condition/crohn-disease#genes
3. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci 1989.
4. A Ilnikis, LA Dieleman, HW Barkema et al. Environment and the Inflammatory Bowel Disease. Can J Gastroenterol 2013.
5. www.nhs.uk/Conditions/Crohns-disease/Pages/Symptoms.aspx
6. crohns.org.uk/crohns_disease/investigations-into-crohns-disease
7. crohns.org.uk/crohns_disease/drug-treatment
8. Efficacy and safety of retreatment with anti–tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Paul Rutgeerts. 1999
9. Surg Clin North Am. 2013 Feb;93(1):167–85. doi: 10.1016/j.suc.2012.09.002. Epub 2012 Oct 24. Surgical management of Crohn's disease. Lu KC, Hunt SR.
10. Yamamoto T. Factors affecting recurrence after surgery for Crohn's disease. World J Gastroenterol. 2005;11:3971–3979
11. International Journal of Gynecology & Obstetrics. Volume 58, Issue 2, August 1997, Pages 229–237. Fertility and pregnancy in inflammatory bowel disease. M. Hudson, B. Flett, T.S. Sinclair, RW. Brunt, A. Templeton.
12. World J Gastroenterol. 2012 April 21; 18(15): 1723–1731. Epidemiology and clinical course of Crohn's disease: Results from observational studies. Øistein Hovde and Bjørn A Moum

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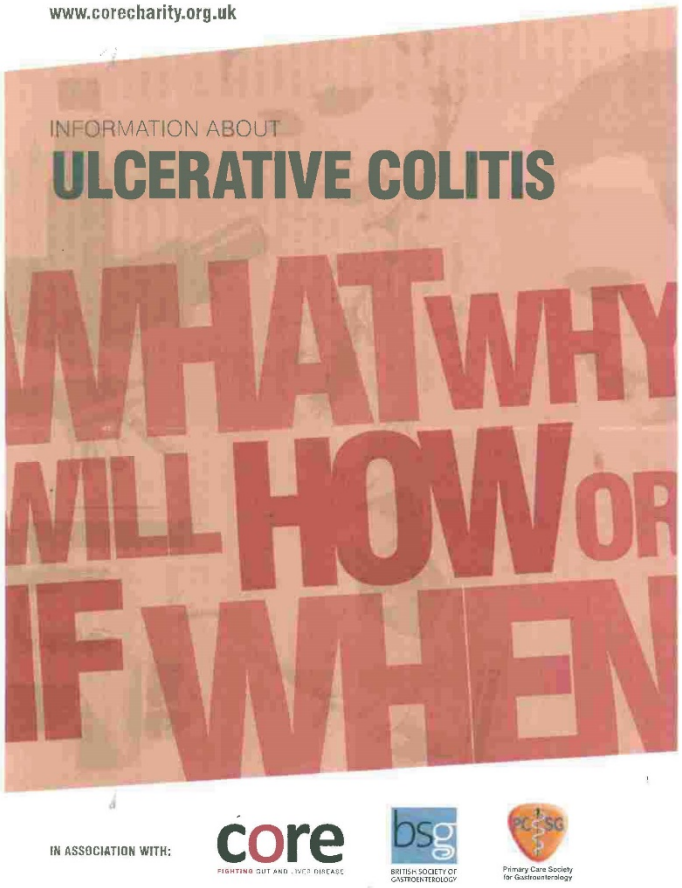
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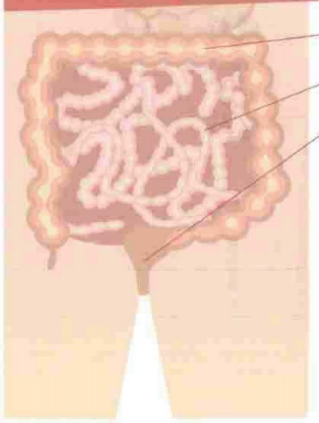
ULCERATIVE COLITIS

Ulcerative Colitis (UC) is a disease of the rectum and the colon (otherwise known as the large intestine). It is one of the two conditions that are known as Inflammatory Bowel Diseases (IBD) – the other being Crohn's Disease.

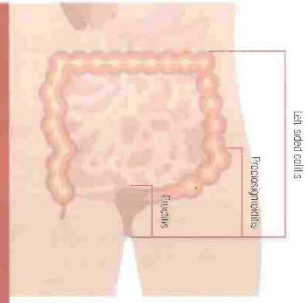
Any medical term that ends in -itis means that there is inflammation or damage to that part of the body. The term 'colitis' means the colon has become inflamed and, if this becomes severe enough, the lining of the colon can be breached and ulcers may form. The term 'ulcerative colitis' can seem confusing, as many patients never actually develop ulcers because the degree of inflammation is not that advanced. It's best to think of UC as a disease in which there is wide variation in the amount of inflammation so that in mild cases the colon can look almost normal but when the inflammation is bad, the bowel can look very diseased and can contain ulcers.

One study, from the UK, found that UC affects around 14 people per 100,000 with average incidence being around 10 per 100,000 people[1]. The peak age of incidence between 15-25 years old with a smaller peak occurring between the age of 55 and 65 years old but it can occur at any age[2]. It is more common in certain populations[3] (Ashkenazi Jews and South Asians).



HOW MUCH OF THE COLON CAN BECOME DISEASED?

Ulcerative colitis[4] always affects the rectum – that part of the large bowel, which lies just inside the anus. Sometimes, the inflammation is limited just to the rectum, which is known as proctitis, as seen in the picture below. However, the inflammation can involve a variable length of the colon. When the whole colon is affected, this is called pan-colitis or total colitis. We don't know why the amount of inflamed bowel varies so much between individuals.



WHY DOES UC HAPPEN?

We don't know the cause of ulcerative colitis – it is most likely to result from a combination of factors[5]. Doctors have looked hard to find either an infection or potential dietary causes, but have drawn a blank. For a while it seemed that ulcerative colitis might be one of the diseases where the body seems to be attacking itself. We now think that this is very unlikely, but there is no doubt that something must be causing damage to the lining of the large intestine.

Most doctors now think the cause of UC relates to how patients react to the apparently harmless bacteria that everyone has in their colon. In most people, the bacteria that live in the colon do not cause any damage and indeed can be quite useful. They are sometimes known as 'friendly' bacteria. However, patients with ulcerative colitis don't see them as being at all friendly and when the lining of the large intestine goes into battle with these bacteria, the result is that the inflammation starts[4]. An enormous research effort is under way to find out why patients with ulcerative colitis appear to react badly to bacteria that don't normally cause any harm in others.

WHAT ARE THE SYMPTOMS?

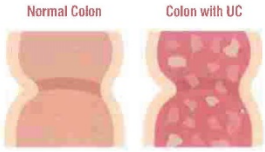
The three most common symptoms of UC are:

- Diarrhoea,
- Bleeding from the back passage;
- Pain in the abdomen.[6]

However, symptoms do vary from one patient to the next, so many people do not have all three of these together. For example, some patients may just notice that they pass blood when they open their bowels. Others may not have diarrhoea but feel rather constipated. To a certain extent, the symptoms depend on how much inflammation there is and how much of the colon is affected by the disease. Weight loss is a feature of severe disease.

For some people, the symptoms can be a nuisance but may be tolerable. For others, the condition can really interfere with day-to-day life, which can become organized around visits to the toilet. It is not only just the number of times this can happen each day but the hurry in which some patients need a toilet can also be extremely distressing. As symptoms are often at their worst in the morning, this can mean the start of the day can be quite an ordeal.

Some patients pass considerable quantities of mucus when they open their bowels whilst others can be greatly troubled by wind. Many patients can just feel tired, not their usual self and they (or their family and friends) notice they have become just plain irritable. Sometimes there are symptoms outside the abdomen – such as sore eyes, painful joints and skin rashes.



WHAT IS YOUR DOCTOR LIKELY TO DO?

Doctors use three separate steps to come to a precise diagnosis. Firstly, they will listen to your symptoms and ask you questions about your health. This is called 'taking your history'. Secondly they will want to examine you to see if they can detect any 'signs' that something is wrong. For example, they may notice that you are unusually pale (which might suggest you are anaemic) or, perhaps, you seem rather tender when the doctor presses gently on your tummy (which can be a sign of inflammation in the colon). Thirdly, they will probably ask you to undergo some tests.

WHAT TESTS MIGHT I NEED?

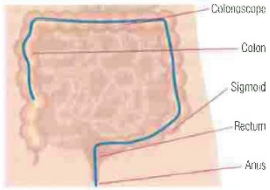
If your doctor thinks you might have ulcerative colitis, you will probably be asked to have tests of your blood, your motions and your intestines. Blood tests will show if you are anaemic and whether your illness has caused the level of protein to fall. In general, the greater the degree of anaemia and the lower the protein level, the more severe the inflammation is likely to be. Doctors also use special blood tests called ESR and CRP to give a measure of the degree of inflammation. You may be asked to give small samples of your bowel motions so as to be sure there are no signs of any bowel infection.

WHAT OTHER INVESTIGATIONS COULD BE NECESSARY?

The most important investigation is to look directly at the lining of the large intestine. Sometimes the doctor will choose to carry out such an examination in the outpatient clinic. This is known as sigmoidoscopy and has the convenience of you not having to take any special preparations beforehand, as the doctor will only look at the rectum and perhaps the lowest part of the sigmoid colon. Sometimes biopsies (tiny pieces of the lining of the bowel) are taken at the time of sigmoidoscopy and analysed under a microscope in a laboratory. However, sooner or later the doctor will want to see more of your bowel and the best way to do this is by the technique of colonoscopy.

WHAT IS A COLONOSCOPY?

A colonoscope is a tube, which is long enough but sufficiently flexible to be passed through your back passage along the whole length of the colon. You will be asked to follow a special diet and also to take some quite powerful laxatives just before the test to make sure the bowel is entirely empty. You will be offered an injection beforehand to minimise any discomfort that might be caused – but an anaesthetic is only needed very rarely. It is usually possible to see all of the rectum and the colon and it is likely that the doctor will take some biopsies to study after the procedure has finished. A colonoscopy will confirm the diagnosis of ulcerative colitis and provide detailed information on the extent and severity of inflammation in the intestine. Biopsies are often used to confirm this diagnosis.



WHAT TREATMENT MIGHT I EXPECT?

Since the cause of ulcerative colitis is not known there are two important implications for treatment. Firstly, until the cause is discovered it is most unlikely that there will be a medicine that will cure the condition. Secondly, all treatments available at present are directed towards reducing the amount of inflammation in the bowel.

Fortunately, for most patients with UC, medicines prove effective although it is possible that your treatment may need to be varied to find the drugs that work best for you. Your doctors will firstly try to find a treatment that will bring the disease under control. Then they will work on finding a treatment to keep you that way.

BRINGING ULCERATIVE COLITIS UNDER CONTROL

Your doctor may refer to this phase as "Putting your disease in to remission" and almost always, the choice of treatment will depend on the extent and severity of the inflammation within the large bowel. If the inflammation is confined to the rectum ('proctitis'), it is quite possible the doctor will recommend a medication that you will need to insert into the rectum through the back passage. Although the thought of this can be unpleasant, it can be helpful to appreciate that giving your treatment this way does mean that the therapy is accurately directed right against the inflamed part of your bowel. Treatment can be given as suppositories or as enemas. Enemas can also be useful if the disease involves more of the large bowel than just the rectum alone, but if the inflammation in the bowel is extensive enough to affect more than half of the colon, it is also likely that you will be prescribed tablets to take by mouth. There are some special dietary measures' that can be undertaken that may prevent relapses and be beneficial to UC patients such as limiting dairy intake and taking fish oils.

WHAT DRUGS ARE AVAILABLE?

The anti-inflammatory drugs include aminosalicylates in milder cases and steroids if the inflammation is more severe. There are a variety of aminosalicylates (such as mesalazine8) and your doctors will choose the preparation they feel is best for you. They are usually extremely safe to use. Steroids (such as prednisolone9) are more powerful but doctors are rather reluctant for patients to take these drugs for more than a few weeks at a time because of the risk of side effects. However, most patients do get better with these treatments.

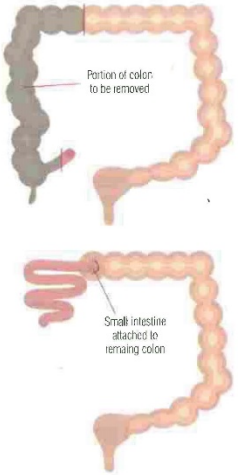
HOW MIGHT A RELAPSE BE PREVENTED?

Your doctor will discuss alternative ways of preventing relapse10, and good control of your condition will depend on a partnership between you, your GP and your Specialist. Regular review is important to ensure that you are on the best possible treatment and that your symptoms are well controlled. Aminosalicylates are helpful and may reduce cancer risk. If possible, doctors try to avoid giving patients with UC steroids in the long term because of the side effects. As an alternative, the possibility of taking azathioprine may be discussed with you. This calms down the immune system and, although only weakly effective against active disease, it has proved most useful in preventing relapses. This drug does need close monitoring in the first few weeks of treatment in order to detect side effects although most people do not have any problems when they take it.

WHAT WILL HAPPEN IF TREATMENT WITH MEDICINES FAILS?

Doctors try hard to control UC with drugs and medicines. But in the occasional situation that these don't help, or should you become very unwell, you may be offered admission to hospital11. If the disease still fails to respond to treatment, it is likely that a surgical operation to remove part or all of the colon (called a colectomy) will be considered. Although surgery can seem a drastic step, it does cure the disease (if you don't have a colon, you can't have colitis). In former times, colectomy used to mean

needing a bag to wear on your tummy. Nowadays, it is usually possible to remove the diseased colon and rectum and then construct a pouch of small intestine that acts very much like the rectum giving no need for a bag.



CAN ULCERATIVE COLITIS CAUSE COMPLICATIONS?

A small number of patients do have complications that relate to UC in their skin, eyes, joints or liver as a result of their disease. When you attend the hospital, you will be monitored to see if any of these complications do develop so that they can be treated. You may have heard that patients with UC run an increased risk of getting bowel cancer[12]. The bad news is that this is true; the good news is that bowel cancer is still an uncommon complication of the disease and that your doctor will keep an eye on your bowel (quite literally; by performing colonoscopy at regular intervals) to detect pre-malignant changes in the lining of the bowel at a stage well before cancer has yet developed.

AM I LIKELY TO DIE OF THIS DISEASE?

No.

WHAT RESEARCH IS NEEDED?

We must find the cause of the disease. Until then, we need to know as much as possible about all the steps that lead the inflammation in UC to develop. This will lead to the development of better drugs to control the condition. Being able to target drugs directly against the causes of the inflammation in UC is proving to be very valuable in developing new treatments.

The Crohns and Colitis UK group have many detailed leaflets on living with UC (and Crohns) especially related to employment, disability and fertility. They also provide information about patient groups and volunteering opportunities. These are found at **www.crohnsandcolitis.org.uk**.

REFERENCES:

1. Ulcerative Colitis. Silvio Danese, M.D., and Claudio Fiocchi, M.D. N Engl J Med 2011; 365:1713-1725
2. Basson M et al. Ulcerative Colitis. Medscape. May 2011
3. Mangat et al Can J Gastroenterol. 2011 February; 25(2): 73-77
4. www.nhs.uk/conditions/ulcerative-colitis/Pages/Introduction.aspx
5. Sartor B Gastroenterology Clinics of North America [1995, 24(3):475-507]
6. www.patient.co.uk/health/ulcerative-colitis
7. www.ulcerativecolitis.org.uk/dietarychanges.htm
8. www.ulcerativecolitis.org.uk/medications/asacol_mesalazine.htm
9. www.ulcerativecolitis.org.uk/medications/steroids.htm
10. publications.nice.org.uk/ulcerative-colitis-cg166/key-priorities-for-implementation#inducing-remission-step-1-therapy-for-mild-to-moderate-ulcerative-colitis
11. Mowat C, Cole A, Windsor A, et al. Gut (2011). doi:10.1136/gut.2010.224154
12. www.cancerresearchuk.org/cancer-help/type/bowel-cancer/about/risks/high-risk-groups-for-bowel-cancer

YOU CAN HELP COMBAT GUT AND LIVER DISEASE BY MAKING A DONATION.

Conditions that affect the gut, the liver and the pancreas (collectively known as digestive diseases) are widespread but little known. They can cause significant health problems for people who live with them and, sadly, they are a factor in 1 in 8 UK deaths. Core is the only national charity working to change this by fighting all digestive diseases. As a charity, Core:

- Supports important medical research that looks for cures and for ways of improving the lives of patients;
- Provides evidence-based information that enables patients and families to understand and control their condition;
- Works to raise awareness of these conditions, their symptoms and impact.

THERE ARE MANY WAYS YOU CAN SUPPORT OUR WORK NOW:

- Call us on **020 7486 0341**
- Text **CORE14** plus your donation amount to **70070**
- Complete the form overleaf and return it to us
- Donate via our website at **www.corecharity.org.uk**

You can find more information about digestive diseases and about Core's work by visiting our website at **www.corecharity.org.uk** or by calling **020 7486 0341** during office hours.

This leaflet was published by Core in 2014 and will be reviewed during 2016. If you are reading this after 2016 some of the information may be out of date. This leaflet was written under the direction of our Medical Director and has been subject to both lay and professional review.

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Please contact us if you believe any information in this leaflet is in error.

Our Vision To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS Foundation Trust

University of East Anglia

DELEGATION LOG

(Site signatures and delegation of responsibility log)

Study:	N-ASPIRE CT Strategy
Principle investigator:	Chong Seng Edwin Lim
Site:	Norfolk and Norwich University Hospital

Legend		
Use this legend to complete the General Duties column. For each individual listed in the Name column, enter the letter(s) (eg. a c, e) from the legend below that correspond to their protocol-related duties in the General Duties Column. If there are significant protocol related duties that are not already included in the legend, add them in the empty spaces provided below.		
A. Identifying participant.	B. Providing/verifying radiology specific data for consented enrolled patients.	C. Phase 1 activities – receipt and processing of returned questionnaires.
D. Phase 2 activities – checking eligibility criteria.	E. Phase 2 activities – telephone contact & invitation.	F. Phase 2 activities – informed consent process.
G. Phase 2 activities – clinical assessment.	H. Phase 2 activities – request of investigations, review & interpretation of results.	I. Phase 1/2 activities – data entry in paper and electronic database.
J. Process of Rheumatologist Verified Diagnosis (PVD)	K. Phlebotomy	L. Administration (printing, sending mail, typing letters, etc)
M.	N.	O.

Name (please print)	Trial Role	General Duties (see legend)	Initials	Signature	Date of Duties		Principal Investigator Signature	Date of PI Signature
					From (dd-MMM-yyyy)	To (dd-MMM-yyyy)		

Statement					
I have reviewed the information on this log and have found it to be accurate. All delegated duties were performed with my authorisation.					
Principle Investigator Signature:		Site Start Date:		Site End Date:	

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

a **If you are currently taking medication for your AS, please give the name and dose that is on the bottle/packet.**

b **Please mark on the line below to indicate the effectiveness of the medication in relieving your symptoms.**

NO EFFECT _____ VERY EFFECTIVE

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *past week*

SCORE/10

1 **How would you describe the overall level of fatigue/tiredness you have experienced?**

NONE _____ VERY SEVERE

2 **How would you describe the overall level of AS neck, back or hip pain you have had?**

NONE _____ VERY SEVERE

3 **How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?**

NONE _____ VERY SEVERE

4 **How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?**

NONE _____ VERY SEVERE

5 **How would you describe the overall level of discomfort you have had from the time you wake up?**

NONE _____ VERY SEVERE

6 **How long does your morning stiffness last from the time you wake up?**

0 ½ 1 1½ 2 or more hours

MEAN OF 5&6

TOTAL OF 1 TO 4 ADDED TO MEAN OF 5&6 (TOTAL OUT OF 50)

TOTAL / 5 (BASDAI SCORE)

BASDAI Score Calculation

Score from all questions are calculated using a ruler. The mean measurement (score) of questions 5 and 6 is added to the scores from questions 1 to 4. This total is then divided by 5 to give the average. This is the BASDAI score. The higher the BASDAI score, the more severe the patients disability due to their AS.

Please Note:
When using visual analog scales of a set length (10cm in the case of the Bath Indices), great care must be taken in reproducing assessment paperwork as repeated photocopying, for example, may distort the length of the lines and therefore will affect the accuracy of the scoring.

Referrence: Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994 Dec;21(12):2286–91.

The Bath Ankylosing Spondylitis Functional Index (BASFI)

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *past week*

HOW DO YOU FIND:	score out of 10
1 Putting on your socks or tights without help or aids (eg sock aid)? EASY _____ IMPOSSIBLE	
2 Bending forward from the waist to pick up a pen from the floor without an aid? EASY _____ IMPOSSIBLE	
3 Reaching up to a high shelf without help or aids (eg Helping Hand)? EASY _____ IMPOSSIBLE	
4 Getting out of an arm-less dining chair without using your hands or any help? EASY _____ IMPOSSIBLE	
5 Getting up off the floor - without help - from lying on your back? EASY _____ IMPOSSIBLE	
6 Standing unsupported for ten minutes without discomfort? EASY _____ IMPOSSIBLE	
7 Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)? EASY _____ IMPOSSIBLE	
8 Looking over your shoulder without turning your body? EASY _____ IMPOSSIBLE	
9 Doing physically demanding activities (eg physio exercises, gardening, sport)? EASY _____ IMPOSSIBLE	
10 Doing a full day's activities at home or at work? EASY _____ IMPOSSIBLE	
TOTAL OUT OF 100	
TOTAL / 10 (BASFI SCORE)	

BASFI Score Calculation

Score from all questions are calculated using a ruler and added. This figure is divided by 10 to obtain an average. This is the BASFI score. The higher the BASFI score, the more severe the patient's limitation of function due to their AS.

Please Note:
When using visual analog scales of a set length (10cm in the case of the Bath Indices), great care must be taken in reproducing assessment paperwork as repeated photocopying, for example, may distort the length of the lines and therefore will affect the accuracy of the scoring.

Reference: Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994 Dec;21(12):2281–5.

The Bath Ankylosing Spondylitis Global Score (BAS-G)

	TOTAL / 10
How have you been over the last week? VERY GOOD _____ VERY BAD **How have you been over the last six months?** VERY GOOD _____ VERY BAD	
TOTAL OUT OF 20	
TOTAL / 2 (BAS-G SCORE)	

BAS-G Score
Scores from the 2 questions are calculated using a ruler and added. This figure is divided by 2 to obtain an average, this is the BAS-G score. The higher the BAS-G score, the more severe the effect of AS on the patient's life.

Please Note:
When using visual analog scales of a set length (10cm in the case of the Bath Indices), great care must be taken in reproducing assessment paperwork as repeated photocopying, for example, may distort the length of the lines and therefore will affect the accuracy of the scoring.

Referrence: Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 1996 Jan;35(1):66–71.

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TRAINING LOG
(Including Delegation Checklist)

Study:	N-ASPIRE CT Strategy
Principle investigator:	Chong Seng Edwin Lim
Site:	Norfolk and Norwich University Hospital

Training Topics / Checklist
1. Curriculum vitae (CV)
2. Good Clinical Practice (GCP)
3. Review of Study Protocol
4. Identifying participant and providing/verifying radiology specific data for consented enrolled patients
5. Phase 1 activities – receipt and processing of returned questionnaires, data entry in electronic database
6. Phase 2 activities – checking eligibility criteria, telephone contact & invitation, informed consent process, clinical assessment, request of investigations, review & interpretation of results, data entry in paper and electronic database
7. Process of Physician Verified Diagnosis (PVD) and familiarisation with Rheumatologist Diagnosis Sheet (RDS)
8. Other (write in):
9. Other (write in):
10. Other (write in):

Method of Training / Evidence	
1. Document(s) showing previous achievement as evidence	5. Self Study – Additional protocol specific summary materials
2. Live Training & Coaching by PI	6. Other (Explain):
3. Self Study – Paper protocol review	7. Other (Explain):
4. Self Study – Electronic protocol review	8. Other (Explain):

Name and Title of Trainee	Trainee initials, signature and date	List of topics numbers covered during training	Method of training	Comments (e.g. Date of CV & GCP, etc)	Confirmation by PI (initials & date)

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CONSULTANTS
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Direct dial 1: 01603 287621
Direct dial 2: 01603 647835
Switchboard: 01603 286286

Patient Name:
Address:
Date of Birth:
NHS Number:
Hospital Number:

Attach Patient Label or Type in template

What proportion of patients with Inflammatory Bowel Disease have Axial Spondyloarthritis – An imaging referral strategy utilising Computed Tomography defined Sacroiliitis [Norfolk - Axial SPa Ibd REferral Computer Tomographic Strategy (N-ASPIRE CT Strategy)]

Dear (Insert Patient's Name),

Insert Appropriate Details e.g. appointment details, result letter, etc

Yours sincerely,

Dr Chong Seng Edwin Lim
Senior Research Fellow (Rheumatology)

Professor Karl Gaffney
Rheumatology Consultant

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CT SCREENING TOOL

POSITIVE CTSI	• **The presence of one or more of the following criterion.**
Criteria	1. **Sacroiliac joint ankylosis** 2. **Total erosion score (TES) of ≥3**

Term	Definitions
Surfaces and anatomy of sacroiliac joint	• 4 surfaces – right iliac, left iliac, right sacral, left sacral • Anatomy of the sacroiliac joint (SIJ) – Erosions are recorded only if present along the cartilaginous component. Lesions along the fibrous component are not counted.
Erosions	• Erosions had to have a clear break in subchondral bone with a minimum depth of 2mm. o Erosions are breaks seen on either the axial or coronal view o The erosion depth is to be rounded down to 1mm if measurement is <=1.49mm and rounded up to 2mm if measurement is >=1.5mm o Erosions are included if they involve the joint proper. Bony defects/irregularity seen at the inferior margin of the bony pelvis are excluded. • Large erosions are erosions seen on more than 1 slice. • Counting the maximum number of erosions from the worst slice from each articular surface. • Total erosion score (TES) is sum of the maximum number of erosions from the worst slice from each articular surface • Note: o Osseous abnormalities at the transition point from cartilaginous to fibrous compartment are not scored as erosions. o Subchondral cysts are radiolucent lesions without a clear break in the subchondral bone and lesions where the break was ambiguous are not included.
Ankylosis	• Ankylosis is defined as contiguous bone marrow between the ilium and sacrum > 1 cm in length within the cartilage compartment of the joint. • If a joint was scored as having ankylosis, neither erosion number nor presence of sclerosis was noted because these changes would be obscured by the ankylosis.
Sclerosis	• Sclerosis is only read from the coronal view and defined as an increase in bone density of at least 1cm in length parallel to the joint line when compared to the midline of the sacrum and scored as present/ absent. • The depth of sclerosis is evaluated on the slice with the longest visible cartilage length and noted as extending either >3mm or >5mm perpendicular to the joint line. • Sclerotic segments are only measured in areas of homogeneous density as patchy density is poorly reproducible. • The initial 5mm at the cranial and caudal ends of the joint where there can be a normal increase in density are not scored.

Reference & Adaptation:
• Chan J, Sari I, Salonen D, Inman RD, Haroon N. Development of a Screening Tool for the Identification of Sacroiliitis in Computed Tomography Scans of the Abdomen. J Rheumatol. 2016;9.

Glossary

AAU: acute anterior uveitis
AS: ankylosing spondylitis
ASAS: assessment of spondyloarthritis international society
AS-IBD: ankylosing spondylitis-related inflammatory bowel disease
axSpA: axial spondyloarthritis
axSpA-IBD: axial spondyloarthritis related inflammatory bowel disease
BASDAI: bath ankylosing spondylitis disease activity index
BASFI: bath ankylosing spondylitis functional index
BASG: bath ankylosing spondylitis patient global score
BASMI: bath AS metrology index
CARD15: caspase activating recruitment domain 15
CBP: chronic back pain
CD: crohn's disease
CRP: c-reactive protein
CT: computed tomography
CTSI: computed tomography defined Sacroiliitis
EMM: extra-musculoskeletal manifestations
ESR: erythrocyte sedimentation rate
ESSG: European Spondyloarthropathy Study Group
GWAS: genome-wide association studies
HLA-B27: human leukocyte antigen B27
IBD: inflammatory bowel disease
IBP: inflammatory back pain
JAK: janus kinase
LoC: level of confidence
MASES: maastricht ankylosing spondylitis enthesitis score
mNYC: modified New York Criteria
MRI: magnetic resonance imaging
MSK: musculoskeletal
N-ASPIRE: Norfolk - Axial SPa Ibd REferral
NASS: national axial spondyloarthritis society
NICE: national institute for health and care excellence
NOD2: nucleotide-binding oligomerization domain-2
nr-axSpA: non-radiographic axial spondyloarthritis
OMERACT: outcome measures in rheumatoid arthritis clinical trials
PsA: psoriatic arthritis
PsO: skin psoriasis
pSpA: peripheral spondyloarthritis
r-axSpA: radiographic axSpA
ReA: reactive arthritis

RVD-axSpA: rheumatologist-verified diagnosis of axial spondyloarthritis
sCBP: self-reported chronic back pain
SpA: spondyloarthritis
SQ: screening questionnaires
TNFi: tumour necrosis factor
UC: ulcerative colitis
X-ray: radiography

Bibliography

1. Lim CSE, Sengupta R, Gaffney K. The clinical utility of human leucocyte antigen B27 in axial spondyloarthritis. Rheumatology 2018;57:959–68.

2. Lim CSE, Hamilton L, Low SBL, Toms A, Macgregor A, Gaffney K. Identifying Axial Spondyloarthritis in Inflammatory Bowel Disease Patients Utilising Computed Tomography. The Journal of Rheumatology [Internet] 2022 [cited 2023 Aug 31];Available from: https://www.jrheum.org/content/early/2022/10/10/jrheum.220362

3. Lim C, Low S, Dhillon B, Azegami S, Toms A, Gaffney K. A Service Evaluation of Reporting Standards of Computer Tomography Defined Sacroiliitis Suggestive of Axial Spondyloarthritis in Inflammatory Bowel Disease Patients Imaged for Non-Musculoskeletal Indications. Arthritis Rheumatol [Internet] 2018 [cited 2020 Jun 7];70 (suppl 9). Available from: https://acrabstracts.org/abstract/a-service-evaluation-of-reporting-standards-of-computer-tomography-defined-sacroiliitis-suggestive-of-axial-spondyloarthritis-in-inflammatory-bowel-disease-patients-imaged-for-non-musculoskeletal-indi/

4. Lim CSE, Tremelling M, Hamilton L, Kim M, Macgregor A, Turmezei T, et al. Prevalence of undiagnosed axial spondyloarthritis in inflammatory bowel disease patients with chronic back pain: secondary care cross-sectional study. Rheumatology 2023;62:1511–8.

5. Lim CSE, Low BLS, Dhillon B, Azegami S, Toms AP, Karl G. O34 Is computed tomography defined sacroiliitis suggestive of axial spondyloarthritis reported in patients with inflammatory bowel disease who are imaged for non-musculoskeletal indications? Rheumatology (Oxford) [Internet] 2019 [cited 2020 Jun 15];58. Available from: https://academic.oup.com/rheumatology/article/58/Supplement_3/kez105.033/5444536

6. Lim CSE, Tremelling M, Hamilton L, Macgregor A, Gaffney K. Sat0380 Enhancing Rheumatology Referrals Among Inflammatory Bowel Disease Patients with Suspected Axial Spondyloarthritis. Annals of the Rheumatic Diseases 2020;79:1138–1138.

7. Lim C, Tremelling M, Hamilton L, MacGregor A, Turmezei T, Kim M, et al. Prevalence of Undiagnosed Axial Spondyloarthritis Among Patients with Inflammatory Bowel Disease: A Secondary Care Cross-Sectional Study. ACR Meeting Abstracts [Internet] 2020 [cited 2021 Jun 14];72 (suppl 10). Available from: https://acrabstracts.org/abstract/prevalence-of-

undiagnosed-axial-spondyloarthritis-among-patients-with-inflammatory-bowel-disease-a-secondary-care-cross-sectional-study/

8. Lim CSE, Hamilton L, Low S, Toms A, Macgregor A, Gaffney K. Pos0035 One in Twenty Inflammatory Bowel Disease Patients Who Underwent Abdominopelvic Computed Tomography Have Undiagnosed Axial Spondyloarthritis. Annals of the Rheumatic Diseases 2021;80:223–223.

9. Hamilton L, Barkham N, Bhalla A, Brittain R, Cook D, Jones G, et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology 2017;56:313–6.

10. Keat A, Bennett AN, Gaffney K, Marzo-Ortega H, Sengupta R, Everiss T. Should axial spondyloarthritis without radiographic changes be treated with anti-TNF agents? Rheumatol. Int. 2017;37:327–36.

11. Sieper J, Rudwaleit M, Khan MA, Braun J. Concepts and epidemiology of spondyloarthritis. Best Pract Res Clin Rheumatol 2006;20:401–17.

12. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol 2012;8:262–8.

13. Slobodin G, Eshed I. Non-Radiographic Axial Spondyloarthritis. Isr. Med. Assoc. J. 2015;17:770–6.

14. Lambert RGW, Bakker PAC, van der Heijde D, Weber U, Rudwaleit M, Hermann KG, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann. Rheum. Dis. 2016;75:1958–63.

15. Rudwaleit M, Jurik AG, Hermann KGA, Landewé R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann. Rheum. Dis. 2009;68:1520–7.

16. Rudwaleit M, Landewé R, Heijde D van der, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770–6.

17. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann. Rheum. Dis. 2009;68:777–83.

18. Poddubnyy D. Classification vs diagnostic criteria: the challenge of diagnosing axial spondyloarthritis. Rheumatology (Oxford) 2020;59:iv6–17.

19. Wright V. Seronegative polyarthritis: a unified concept. Arthritis Rheum. 1978;21:619–33.

20. Moll JMH. 'The Leeds Idea': an historical account of the spondarthritis concept. Reumatismo 2007;59.

21. Baraliakos X, Braun J. Spondyloarthritides. Best Practice & Research Clinical Rheumatology 2011;25:825–42.

22. Ashrafi M, Ermann J, Weisman MH. Spondyloarthritis evolution: what is in your history? Current Opinion in Rheumatology 2020;32:321–9.

23. Di Jiang C, Raine T. IBD considerations in spondyloarthritis. Therapeutic Advances in Musculoskeletal 2020;12:1759720X20939410.

24. Baraliakos X, Braun J. Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences? RMD Open [Internet] 2015 [cited 2016 Dec 20];1. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632143/

25. Sieper J, Poddubnyy D. Axial spondyloarthritis. The Lancet 2017;390:73–84.

26. Ritchlin C, Adamopoulos IE. Axial spondyloarthritis: new advances in diagnosis and management. BMJ 2021;m4447.

27. Fragoulis GE, Siebert S. Treatment strategies in axial spondyloarthritis: what, when and how? Rheumatology 2020;59:iv79–89.

28. Capelusnik D, Benavent D, van der Heijde D, Landewé R, Poddubnyy D, van Tubergen A, et al. Treating spondyloarthritis early: does it matter? Results from a systematic literature review. Rheumatology 2023;62:1398–409.

29. Yu W, Feng F, Dion E, Yang H, Jiang M, Genant HK. Comparison of radiography, computed tomography and magnetic resonance imaging in the detection of sacroiliitis accompanying ankylosing spondylitis. Skeletal Radiol. 1998;27:311–20.

30. Bray TJP, Jones A, Bennett AN, Conaghan PG, Grainger A, Hodgson R, et al. Recommendations for acquisition and interpretation of MRI of the spine and sacroiliac joints in the diagnosis of axial spondyloarthritis in the UK. Rheumatology (Oxford) 2019;58:1831–8.

31. Tsoi C, Griffith JF, Lee RKL, Wong PCH, Tam LS. Imaging of sacroiliitis: Current status, limitations and pitfalls. Quant. Imaging Med. Surg 2019;9:318–35.

32. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361–8.

33. Navallas M, Ares J, Beltrán B, Lisbona MP, Maymó J, Solano A. Sacroiliitis associated with axial spondyloarthropathy: new concepts and latest trends. Radiographics 2013;33:933–56.

34. Østergaard M. MRI of the sacroiliac joints: what is and what is not sacroiliitis? Current Opinion in Rheumatology 2020;32:357–64.

35. Eno JJT, Boone CR, Bellino MJ, Bishop JA. The prevalence of sacroiliac joint degeneration in asymptomatic adults. J Bone Joint Surg Am 2015;97:932–6.

36. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int 2003;23:61–6.

37. Pialat JB, Di Marco L, Feydy A, Peyron C, Porta B, Himpens PH, et al. Sacroiliac joints imaging in axial spondyloarthritis. Diagn Interv Imaging 2016;97:697–708.

38. Geijer M, Gadeholt Göthlin G, Göthlin JH. Diagnosis and progression of sacroiliitis in repeated sacroiliac joint computed tomography. Arthritis 2013;2013:659487.

39. Prakash D, Prabhu SM, Irodi A. Seronegative spondyloarthropathy-related sacroiliitis: CT, MRI features and differentials. Indian J Radiol Imaging 2014;24:271–8.

40. Evans J, Sapsford M, McDonald S, Poole K, Raine T, Jadon DR. Prevalence of axial spondyloarthritis in patients with inflammatory bowel disease using cross-sectional imaging: a systematic literature review. Ther Adv Musculoskelet Dis 2021;13:1759720X21996973.

41. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis 2017;11:649–70.

42. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis 2017;11:3–25.

43. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand. J. Gastroenterol. Suppl. 1989;170:2–6; discussion 16-19.

44. Gordon BL. Medicine throughout antiquity. Philadelphia: F.A. Davis; 1949.

45. Gran JT, Husby G. Joint manifestations in gastrointestinal diseases. 1. Pathophysiological aspects, ulcerative colitis and Crohn's disease. Digestive diseases (Basel, Switzerland) 1992;10:274–94.

46. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:65–73.

47. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. Gastroenterology 2012;142:46-54.e42.

48. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford) 2014;53:650–7.

49. de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis research & therapy 2016;18:196.

50. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Journal of Crohn's & colitis 2017;11:631–42.

51. Cooper R, Fraser SM, Sturrock RD, Gemmell CG. Raised titres of anti-klebsiella IgA in ankylosing spondylitis, rheumatoid arthritis, and inflammatory bowel disease. British medical journal (Clinical research ed.) 1988;296:1432–4.

52. Aydin SZ, Atagunduz P, Temel M, Bicakcigil M, Tasan D, Direskeneli H. Anti-Saccharomyces cerevisiae antibodies (ASCA) in spondyloarthropathies: a reassessment. Rheumatology (Oxford) 2008;47:142–4.

53. de Vries M, van der Horst-Bruinsma I, van Hoogstraten I, van Bodegraven A, von Blomberg BME, von Blomberg M, et al. pANCA, ASCA, and OmpC antibodies in patients with ankylosing spondylitis without inflammatory bowel disease. The Journal of rheumatology 2010;37:2340–4.

54. Wallis D, Asaduzzaman A, Weisman M, Haroon N, Anton A, McGovern D, et al. Elevated serum anti-flagellin antibodies implicate subclinical bowel inflammation in ankylosing spondylitis: an observational study. Arthritis research & therapy 2013;15:R166.

55. Ciccia F, Bombardieri M, Principato A, Giardina A, Tripodo C, Porcasi R, et al. Overexpression of interleukin-23, but not interleukin-17, as an immunologic signature of subclinical intestinal inflammation in ankylosing spondylitis. Arthritis & Rheumatism 2009;60:955–65.

56. Ciccia F, Bombardieri M, Rizzo A, Principato A, Giardina AR, Raiata F, et al. Over-expression of paneth cell-derived anti-microbial peptides in the gut of patients with ankylosing spondylitis and subclinical intestinal inflammation. Rheumatology (Oxford, England) 2010;49:2076–83.

57. Ciccia F, Accardo-Palumbo A, Rizzo A, Guggino G, Raimondo S, Giardina A, et al. Evidence that autophagy, but not the unfolded protein response, regulates the expression of IL-23 in the gut of patients with ankylosing spondylitis and subclinical gut inflammation. Annals of the rheumatic diseases 2014;73:1566–74.

58. Dunn ETJ, Taylor ES, Stebbings S, Schultz M, Butt AG, Kemp RA. Distinct immune signatures in the colon of Crohn's disease and ankylosing spondylitis patients in the absence of inflammation. Immunology and cell biology 2016;94:421–9.

59. Romand X, Bernardy C, Nguyen MVC, Courtier A, Trocme C, Clapasson M, et al. Systemic calprotectin and chronic inflammatory rheumatic diseases. Joint Bone Spine 2019;86:691–8.

60. Oktayoglu P, Bozkurt M, Mete N, Caglayan M, Em S, Nas K. Elevated serum levels of calprotectin (myeloid-related protein 8/14) in patients with ankylosing spondylitis and its association with disease activity and quality of life. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 2014;62:880–4.

61. Duran A, Kobak S, Sen N, Aktakka S, Atabay T, Orman M. Fecal calprotectin is associated with disease activity in patients with ankylosing spondylitis., Fecal calprotectin is associated with disease activity in patients with ankylosing spondylitis. Bosn J Basic Med Sci 2016;16, 16:71, 71–4.

62. Benfaremo D, Luchetti MM, Gabrielli A. Biomarkers in Inflammatory Bowel Disease-Associated Spondyloarthritis: State of the Art and Unmet Needs. J Immunol Res [Internet] 2019 [cited 2020 Jan 19];2019. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6589275/

63. Elewaut D. Linking Crohn's disease and ankylosing spondylitis: it's all about genes!, Linking Crohn's Disease and Ankylosing Spondylitis: It's All about Genes! PLoS Genet 2010;6, 6:e1001223–e1001223.

64. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. Best practice & research. Clinical rheumatology 2006;20:451–71.

65. Brakenhoff LKPM, van der Heijde DM, Hommes DW, Huizinga TWJ, Fidder HH. The joint-gut axis in inflammatory bowel diseases. Journal of Crohn's & colitis 2010;4:257–68.

66. Laukens D, Peeters H, Marichal D, Cruyssen BV, Mielants H, Elewaut D, et al. CARD15 gene polymorphisms in patients with spondyloarthropathies identify a specific phenotype previously related to Crohn's disease. Annals of the Rheumatic Diseases 2005;64:930–5.

67. McEwen C, DiTata D, Lingg C, Porini A, Good A, Rankin T. Ankylosing spondylitis and spondylitis accompanying ulcerative colitis, regional enteritis, psoriasis and Reiter's disease. A comparative study. Arthritis and rheumatism 1971;14:291–318.

68. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? Annals of the rheumatic diseases 1998;57:135–40.

69. De Vos M. Review article: joint involvement in inflammatory bowel disease. Alimentary pharmacology & therapeutics 2004;20.

70. Mielants H, Veys EM, Cuvelier C, de Vos M. Ileocolonoscopic findings in seronegative spondylarthropathies. British journal of rheumatology 1988;27.

71. Mielants H, Veys EM, Cuvelier C, De Vos M, Goemaere S, De Clercq L, et al. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. The Journal of rheumatology 1995;22:2279–84.

72. MIELANTS H, VEYS EM, VOS MD, CUVELIER C, GOEMAERE S, CLERCQ LD, et al. The Evolution of Spondyloarthropathies 1n Relation to Gut Histology. I. Clinical Aspects. The Journal of Rheumatology :7.

73. MIELANTS H, VEYS EM, CUVELIER C, VOS MD, GOEMAERE S, DECLERCQ L, et al. The Evolution of Spondyloarthropathies 1.n Relation to Gut Histology. II. Histological Aspects. The Journal of Rheumatology :6.

74. Vavricka SR, Scharl M, Gubler M, Rogler G. Biologics for extraintestinal manifestations of IBD. Current drug targets 2014;15:1064–73.

75. Wu D, Guo YY, Xu NN, Zhao S, Hou LX, Jiao T, et al. Efficacy of anti-tumor necrosis factor therapy for extra-articular manifestations in patients with ankylosing spondylitis: a meta-analysis. BMC musculoskeletal disorders 2015;16:19.

76. Braun J, Kiltz U, Heldmann F, Baraliakos X. Emerging drugs for the treatment of axial and peripheral spondyloarthritis. Expert opinion on emerging drugs 2015;20:1–14.

77. Juillerat P, Manz M, Sauter B, Zeitz J, Vavricka SR, Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology. Therapies in Inflammatory Bowel Disease Patients with Extraintestinal Manifestations. Digestion 2020;1–15.

78. Ben Nessib D, Ferjani H, Maatallah K, Rahmouni S, Kaffel D, Hamdi W. Update on therapeutic management of spondyloarthritis associated with inflammatory bowel disease. Clin Rheumatol [Internet] 2020 [cited 2020 Nov 10];Available from: http://link.springer.com/10.1007/s10067-020-05136-x

79. Fauny M, Moulin D, D'Amico F, Netter P, Petitpain N, Arnone D, et al. Paradoxical gastrointestinal effects of interleukin-17 blockers. Annals of the Rheumatic Diseases 2020;79:1132–8.

80. Sieper J, Poddubnyy D, Miossec P. The IL-23–IL-17 pathway as a therapeutic target in axial spondyloarthritis. Nat Rev Rheumatol 2019;15:747–57.

81. Gracey E, Vereecke L, McGovern D, Fröhling M, Schett G, Danese S, et al. Revisiting the gut–joint axis: links between gut inflammation and spondyloarthritis. Nat Rev Rheumatol [Internet] 2020 [cited 2020 Jul 22];Available from: http://www.nature.com/articles/s41584-020-0454-9

82. Siebert S, Millar NL, McInnes IB. Why did IL-23p19 inhibition fail in AS: a tale of tissues, trials or translation? 2018;0:4.

83. Salvarani C, Fries W. Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease. World journal of gastroenterology 2009;15:2449–55.

84. Rodríguez-Reyna TS, Martínez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. World journal of gastroenterology 2009;15:5517–24.

85. Ansell BM, Wigley RAD. Arthritic Manifestations in Regional Enteritis *. Ann Rheum Dis 1964;23:64–72.

86. de Vlam K, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. The Journal of rheumatology 2000;27:2860–5.

87. Rios Rodriguez V, Sonnenberg E, Proft F, Protopopov M, Schumann M, Kredel LI, et al. Presence of spondyloarthritis associated to higher disease activity and HLA-B27 positivity in patients with early Crohn's disease: Clinical and MRI results from a prospective inception cohort. Joint Bone Spine 2022;89:105367.

88. Zink A, Listing J, Klindworth C, Zeidler H. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. Ann Rheum Dis 2001;60:199–206.

89. Zhao SS, Pittam B, Harrison NL, Ahmed AE, Goodson NJ, Hughes DM. Diagnostic delay in axial spondyloarthritis: a systematic review and meta-analysis. Rheumatology [Internet] 2021 [cited 2021 Jan 23];Available from: https://doi.org/10.1093/rheumatology/keaa807

90. Seo MR, Baek HL, Yoon HH, Ryu HJ, Choi HJ, Baek HJ, et al. Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis. Clin Rheumatol 2015;34:1397–405.

91. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009;60:717–27.

92. Sieper J, Heijde D van der, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Annals of the Rheumatic Diseases 2013;72:815–22.

93. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatology (Oxford) 2015;54:2283–4.

94. Derakhshan MH, Pathak H, Cook D, Dickinson S, Siebert S, Gaffney K. Services for spondyloarthritis: a survey of patients and rheumatologists. Rheumatology (Oxford) 2018;57:987–96.

95. Sepriano AR, Ramiro S, Araújo FC, Machado PM, Rodrigues AM, Gouveia N, et al. Performance of referral strategies for spondyloarthritis: a population-based nationwide study. Rheumatology (Oxford) 2019;58:1086–94.

96. Coath FL, Gaffney K. Inflammatory back pain: a concept, not a diagnosis. Current Opinion in Rheumatology 2021;33:319.

97. Lassiter W, Allam AE. Inflammatory Back Pain [Internet]. StatPearls Publishing; 2019 [cited 2019 Apr 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539753/

98. Sieper J. How to screen for axial spondyloarthritis in primary care? Current opinion in rheumatology 2012;24:359.

99. Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. Ann Rheum Dis 2005;64:659–63.

100. Back Pain Plus [Internet]. NASS [cited 2017 Sep 24];Available from: https://nass.co.uk/get-involved/campaigning/back-pain-plus/

101. Poddubnyy D, van Tubergen A, Landewé R, Sieper J, van der Heijde D, Assessment of SpondyloArthritis international Society (ASAS). Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. Annals of the rheumatic diseases 2015;74:1483–7.

102. Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clinical Medicine 2017;17:65–70.

103. Scarpa R, Caso F, Costa L, Peluso R, Puente AD, Olivieri I. Psoriatic Disease 10 Years Later. The Journal of Rheumatology 2017;44:1298–301.

104. Mishra S, Kancharla H, Dogra S, Sharma A. Comparison of four validated psoriatic arthritis screening tools in diagnosing psoriatic arthritis in patients with psoriasis (COMPAQ Study). British Journal of Dermatology 2017;176:765–70.

105. Urruticoechea-Arana A, Benavent D, León F, Almodovar R, Belinchón I, de la Cueva P, et al. Psoriatic arthritis screening: A systematic literature review and experts' recommendations. PLoS One 2021;16:e0248571.

106. Proft F, Lüders S, Hunter T, Luna G, Rodriguez VR, Protopopov M, et al. Early identification of axial psoriatic arthritis among patients with psoriasis: a prospective multicentre study. Annals of the Rheumatic Diseases 2022;81:1534–40.

107. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis 2015;74:1990–5.

108. Sykes MP, Hamilton L, Jones C, Gaffney K. Prevalence of axial spondyloarthritis in patients with acute anterior uveitis: a cross-sectional study utilising MRI. RMD Open 2018;4:e000553.

109. Variola A, Zanolin ME, Cipriano G, Macchioni P, Martinis F, Pasetti A, et al. The IBIS-Q [IBd Identification of Spondyloarthritis Questionnaire]: A Novel Tool to Detect Both Axial and Peripheral Arthritis in Inflammatory Bowel Disease Patients. Journal of Crohn's and Colitis 2020;14:1680–6.

110. Di Carlo M, Luchetti MM, Benfaremo D, Di Donato E, Mosca P, Maltoni S, et al. The DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire: development and preliminary testing of a new tool to screen patients with inflammatory bowel disease for the presence of spondyloarthritis. Clin Rheumatol 2018;37:1037–44.

111. Benfaremo D, Luchetti MM, Di Carlo M, Laganà B, Picchianti-Diamanti A, Carubbi F, et al. Multicenter Validation of the DETAIL Questionnaire for the Screening of Spondyloarthritis in Patients With Inflammatory Bowel Diseases. J Rheumatol 2021;48:179–87.

112. Hong SJ, Hudesman DP, Scher JU. A Joint Effort: Improving the Identification of Spondyloarthritis in Patients With Inflammatory Bowel Disease. The Journal of Rheumatology 2023;50:855–6.

113. Gotler J, Amitai MM, Lidar M, Aharoni D, Flusser G, Eshed I. Utilizing MR enterography for detection of sacroiliitis in patients with inflammatory bowel disease. J Magn Reson Imaging 2015;42:121–7.

114. Bruining DH, Siddiki HA, Fletcher JG, Tremaine WJ, Sandborn WJ, Loftus EVJ. Prevalence of penetrating disease and extraintestinal manifestations of Crohn's disease detected with CT enterography. Inflamm Bowel Dis 2008;14:1701–6.

115. Paparo F, Bacigalupo L, Garello I, Biscaldi E, Cimmino MA, Marinaro E, et al. Crohn's disease: prevalence of intestinal and extraintestinal

manifestations detected by computed tomography enterography with water enema. Abdom Imaging 2012;37:326–37.

116. Chan J, Sari I, Salonen D, Silverberg MS, Haroon N, Inman RD. Prevalence of Sacroiliitis in Inflammatory Bowel Disease Using a Standardized Computed Tomography Scoring System. Arthritis Care Res (Hoboken) 2018;70:807–10.

117. Chan J, Sari I, Salonen D, Inman RD, Haroon N. Development of a Screening Tool for the Identification of Sacroiliitis in Computed Tomography Scans of the Abdomen. J Rheumatol 2016;43:1687–94.

118. Ossum AM, Palm Ø, Lunder AK, Cvancarova M, Banitalebi H, Negård A, et al. Ankylosing Spondylitis and Axial Spondyloarthritis in Patients With Long-term Inflammatory Bowel Disease: Results From 20 Years of Follow-up in the IBSEN Study. J Crohns Colitis 2018;12:96–104.

119. Back Pain Plus [Internet]. National Axial Spondyloarthritis Society [cited 2020 Jun 22];Available from: http://https://nass.co.uk/homepage/health-professionals/back-pain-plus/

120. Stolwijk C, Essers I, van Tubergen A, Boonen A, Bazelier MT, De Bruin ML, et al. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. Annals of the rheumatic diseases 2015;74:1373–8.

121. Forster D, Warburton L, O'Flynn N. Diagnosis and management of spondyloarthritis in the over-16s: NICE guideline. Br J Gen Pract 2018;68:346–7.

122. Hamilton L, Macgregor A, Newman D, Belkhiri A, Toms A, Gaffney K. Validation of a patient self-reported screening questionnaire for axial spondyloarthropathy in a UK Population. Spine 2013;38:502–6.

123. Heuft-Dorenbosch L, Spoorenberg A, Tubergen A van, Landewé R, Tempel H van der, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Annals of the Rheumatic Diseases 2003;62:127–32.

124. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J. Rheumatol. 1994;21:1694–8.

125. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J. Rheumatol. 1994;21:2286–91.

126. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J. Rheumatol. 1994;21:2281–5.

127. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br. J. Rheumatol. 1996;35:66–71.

128. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.

129. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N. Engl. J. Med. 1987;317:1625–9.

130. Hermann KGA, Baraliakos X, van der Heijde DMFM, Jurik AG, Landewé R, Marzo-Ortega H, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. Ann. Rheum. Dis. 2012;71:1278–88.

131. Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). The Journal of rheumatology 2002;29:511–5.

132. Steer S, Jones H, Hibbert J, Kondeatis E, Vaughan R, Sanderson J, et al. Low back pain, sacroiliitis, and the relationship with HLA-B27 in Crohn's disease. J Rheumatol 2003;30:518–22.

133. van Erp SJ, Brakenhoff LK, van Gaalen FA, van den Berg R, Fidder HH, Verspaget HW, et al. Classifying Back Pain and Peripheral Joint Complaints in Inflammatory Bowel Disease Patients: A Prospective Longitudinal Follow-up Study. J Crohns Colitis 2016;10:166–75.

134. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA 1977;237:2613–4.

135. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum. 2006;54:569–78.

136. Sieper J, van der Heijde D, Landewé R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the

Assessment of SpondyloArthritis international Society (ASAS). Ann. Rheum. Dis. 2009;68:784–8.

137. Queiro R, Maiz O, Intxausti J, de Dios JR, Belzunegui J, González C, et al. Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. Clinical rheumatology 2000;19:445–9.

138. Leclerc-Jacob S, Lux G, Rat AC, Laurent V, Blum A, Chary-Valckenaere I, et al. The prevalence of inflammatory sacroiliitis assessed on magnetic resonance imaging of inflammatory bowel disease: a retrospective study performed on 186 patients. Alimentary pharmacology & therapeutics 2014;39:957–62.

139. Scott WWJ, Fishman EK, Kuhlman JE, Caskey CI, O'Brien JJ, Walia GS, et al. Computed tomography evaluation of the sacroiliac joints in Crohn disease. Radiologic/clinical correlation. Skeletal Radiol 1990;19:207–10.

140. Turkcapar N, Toruner M, Soykan I, Aydintug OT, Cetinkaya H, Duzgun N, et al. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. Rheumatol Int 2006;26:663–8.

141. McEniff N, Eustace S, McCarthy C, O'Malley M, O'Morain CA, Hamilton S. Asymptomatic sacroiliitis in inflammatory bowel disease. Assessment by computed tomography. Clin Imaging 1995;19:258–62.

142. Orchard TR, Holt H, Bradbury L, Hammersma J, McNally E, Jewell DP, et al. The prevalence, clinical features and association of HLA-B27 in sacroiliitis associated with established Crohn's disease. Alimentary pharmacology & therapeutics 2009;29:193–7.

143. Meucci RD, Fassa AG, Faria NMX. Prevalence of chronic low back pain: systematic review. Rev. Saúde Pública [Internet] 2015 [cited 2020 Jul 8];49. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0034-89102015000100408&lng=en&tlng=en

144. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379–90.

145. Hausmann D, Kiesel V, Zimmerli L, Schlatter N, von Gunten A, Wattinger N, et al. Sensitivity for multimorbidity: The role of diagnostic uncertainty of physicians when evaluating multimorbid video case-based vignettes. PLoS One 2019;14:e0215049.

146. Guillo L, Abreu M, Panaccione R, Sandborn WJ, Azevedo VF, Gensler L, et al. Endpoints for extraintestinal manifestations in inflammatory bowel

disease trials: the EXTRA consensus from the International Organization for the Study of Inflammatory Bowel Diseases. The Lancet Gastroenterology & Hepatology 2022;7:254–61.

147. Zakeri N, Pollok RC. Diagnostic imaging and radiation exposure in inflammatory. 22:15.

148. Govani SM, Higgins PDR, Rubenstein JH, Stidham RW, Waljee AK. CT utilization abruptly increases at age 18 among patients with inflammatory bowel diseases in the hospital. PLOS ONE 2018;13:e0195022.

149. Naidu J, Wong Z, Palaniappan S, Ngiu CS, Ali RAR. Radiation Exposure in Patients with Inflammatory Bowel Disease: a Fourteen-Year Review at a Tertiary Care Centre in Malaysia. Asian Pacific Journal of Cancer Prevention [Internet] 2017 [cited 2018 Aug 20];Available from: http://journal.waocp.org/article_46092.html

150. Kandel R, Merlano Maria, Tan P, Brar G, Mallick R, Macdonald B, et al. Persistently High Rates of Abdominal Computed Tomography Imaging Among Patients With Inflammatory Bowel Disease Who Present to the Emergency Department. Journal of the Canadian Association of Gastroenterology 2023;6:64–72.

151. Evans J, Raine T, Mcdonald S, Poole K, Samworth R, Riede P, et al. POS0965 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). Annals of the Rheumatic Diseases 2022;81:789–90.

152. Carubbi F, Alunno A, Viscido A, Baraliakos X, Mariani FM, Di Ruscio E, et al. SpA plus IBD or IBD plus SpA: Does commutative property apply? Autoimmunity Reviews 2023;22:103443.

153. Barnett R, Gaffney K, Sengupta R. Diagnostic delay in axial spondylarthritis: A lost battle? Best Practice & Research Clinical Rheumatology 2023;37:101870.

154. Eddison J, Selvarajah U, Webb D, Sengupta R, Selinger C. Early recognition of axial spondyloarthritis in patients with inflammatory bowel disease. 2023;