Improving the Diagnosis and Early referral of patients with AxiaL spondyloarthritis: BACK Pain referral pAthway from Community to Specialist care (IDEAL - BACKPACS):

Work-package 2

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STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Ali Alshukry
Head of Research Integrity, Risk & Compliance &
Interim Head of Research Governance
University of Nottingham
E-floor, Yang Fujia Building
Jubilee Campus
Wollaton Road
Nottingham
NG8 1BB
sponsor@nottingham.ac.uk

Chief investigator:

Prof Jon Packham
Clinical Rheumatologist
Rheumatology Department, Haywood Hospital, Stoke on Trent, Midlands Partnership NHS Foundation Trust
UoN job title: Clinical Associate Professor
Phone: 01782 673722
Email: Jon.Packham@mpft.nhs.uk

Co-investigators:

Dr Timothy Bray	Consultant Radiologist and Honorary Clinical Lecture
University College London	
Centre for Medical Imaging, 2nd floor Charles Bell House, 43 -45 Foley street, W1W 7TS	t.bray@ucl.ac.uk
Dr Adrian Chudyk	NIHR Clinical Lecturer in General Practice
Keele University	01782 733969
School of Medicine, David Weatherall building, Room 1.51, Keele University, Keele, ST5 5BG	a.chudyk@keele.ac.uk
Prof Jane Daniels	Professor of Clinical Trials
University of Nottingham	0115 8231600
Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD	jane.daniels@nottingham.ac.uk
Dr Nicola Goodson	Consultant Rheumatologist
Liverpool University Hospitals NHS Foundation Trust	01515295925
	nicola.goodson@liverpoolft.nhs.uk
Prof Toby Helliwell	Professor in General Practice

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Keele University and Midlands Partnership NHS Foundation Trust	01782 734895
School of Medicine, Keele University, Keele Staffordshire. ST5 5BG	t.helliwell@keele.ac.uk
Prof Sue Jowett	Professor of Health Economics
University of Birmingham	0121 414 7898
Health Economics Unit, Institute of Applied Health Research, IOEM Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT	s.jowett@bham.ac.uk
Prof Sue Mallett	Professor in diagnostic and prognostic medical statistics
University College London	
2nd floor Charles Bell House, 43 -45 Foley Street, W1W 7TS	sue.mallett@ucl.ac.uk
Prof Helena Marzo-Ortega	Consultant Rheumatologist and an Honorary Clinical Associate Professor
Leeds Teaching Hospitals NHS Trust	
NIHR Leeds Biomedical Research Centre, Chapel Allerton Hospital, Chapeltown Rd, Leeds LS7 4SA	H.Marzo-Ortega@leeds.ac.uk
Dr Liz Hartshorne	Senior Trial Manager
University of Nottingham	0115 8231600
Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD	liz.hartshorne@nottingham.ac.uk
Dr Christopher Partlett	Assistant Professor of Medical Statistics
University of Nottingham	0115 8231616
Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD	chris.partlett@nottingham.ac.uk
Dr James Prior	Research Fellow in Epidemiology
Keele University	N/A
School of Medicine, Keele University, Keele, Staffordshire, ST5 5BG	j.a.prior@keele.ac.uk
Prof Yeliz Prior	Professor of Clinical Rehabilitation
University of Salford	0161 2950211
PO.54 Brian Blatchford, Frederick Rd Campus University of Salford, M6 6PU	Y.Prior@salford.ac.uk
Dr Caroline Rick	Associate Professor of Clinical Trials
University of Nottingham	0115 8231600
Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD	caroline.rick@nottingham.ac.uk
Prof Raj Sengupta	Consultant Rheumatologist

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Royal National Hospital for Rheumatic Diseases	
Royal United Hospitals, Bath	rajsengupta@nhs.net
Prof Kay Stevenson	Consultant Physiotherapist
Midlands Partnership NHS Foundation Trust and Keele University	01782 733967
	Kay.Stevenson@mpft.nhs.uk

Study Statistician:

Cydney Bruce
Medical Statistician
Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD

Email: Cydney.bruce1@nottingham.ac.uk

Study Coordinating Centre:

Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD

Email: MS-ideal@exmail.nottingham.ac.uk

Protocol Amendment/Modification

Amendment number	Protocol version number	Type of amendment/ modification	Summary of amendment/modification
MM05	1.3	Minor modification	- Flowchart – amended to reflect that the GP's will not be performing a detailed screening of patients - Section 4.1.1 details of retrospective searches added -Wording in Sections 3.4.1, 3.4.5 and 4.1.2 amended to state that a member of the research team (which may not be the local team) will be calling potentially eligible patients to perform the eligibility assessments -Section 5.1 amended to remove an incorrect reference to the way subgroup analyses will be conducted -Table 5 updated to define the scoring of the physical activity questions on the PROMs questionnaires

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NSA02	1.2	Non-substantial	-Title: correction of typographical error -Flowchart: amended to represent recruitment through retrospective searches -Section 3.4.1 Participant Identification, screening, and recruitment: minor amendment to allow multiple retrospective searches by the GPC -Section 4.1.2 Eligibility and enrolment: reference to enrolment through retrospective searches added -Table 1 Summary of assessments for the study: removing reference to “verbal” agreement -Section 5.2 Sample size and justification: Clarified that aim to recruit up to 900 patients, with 720 complete datasets -Signature pages: Sponsor signature field removed

SYNOPSIS

Title	Improving the Diagnosis and Early referral of patients with AxiaL spondyloarthritis- BACK Pain referral pAthway from Community to Specialist care
Short title	IDEAL – BACKPACS
Chief Investigator	Prof Jon Packham
Objectives	**Co-Primary Objectives** Externally validate the Baraliakos strategy’s predictive performance, including sensitivity, specificity, likelihood ratio, calibration and discrimination. Model an alternative UK-specific axSpA referral strategy using combinations of existing Baraliakos predictors and any additional candidate predictors identified in the IDEAL programme evaluation of existing UK axSpA cohorts with pre-existing ethics. **Secondary Objectives** • Determine the most clinically effective (‘superior’) referral strategy by comparative analysis of the four pre-existing candidate strategies (the Baraliakos, modified Braun, ASAS, and CaFaSpA) and the BACKPACS model. The study team anticipate that this will result in either the BACKPACS or Baraliakos strategy going forward as the ‘pop up’ in a separate implementation study, IDEAL-DIRECTED. • To compare the acceptability and clinical effectiveness of the BACKPACS and Baraliakos referral strategy.

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	• Evaluate the National Axial Spondyloarthritis Society (NASS) patient screening questionnaire to determine whether patient self-assessment has the potential to reduce delays in diagnosis. • Estimate of prevalence of axSpA in a UK primary care CBP population. • Evaluate the individual potential screening variables.
Study Configuration	A prospective diagnostic test accuracy study to include the validation of the existing Baraliakos referral strategy in a primary care cohort.
Setting	Patients will be identified from General Practices (GP) acting as Patient Identification centres (PIC) and then clinically assessed at their local secondary care research centre site (all sited in rheumatology services with strong axSpA expertise).
Sample size estimate	Assuming a 14% axSpA prevalence, and a Baraliakos referral strategy with sensitivity 90% and specificity 65%, a total of 720 patients with index and reference diagnoses will provide over 90% power to detect lower bounds of sensitivity 79% and specificity 58% We aim to recruit a total of up to 900 participants to allow for a 20% drop out.
Number of participants	Up to 900 participants with a requirement of 720 participants with complete screening dataset.
Eligibility criteria	**Inclusion Criteria** • Aged 16-50 years with onset of chronic back (cervical/thoracic/lumbar) pain before 45 years. • Current back pain and at least 3 consecutive months of chronic back pain in the last 12 months. • Ability to provide written/electronic informed consent. • Willingness and ability to undergo all study assessments (i.e. clinical examination, X-ray, Magnetic Resonance Imaging (MRI) and blood sample collection). **Exclusion Criteria** • Existing diagnosis of axial spondyloarthritis (axSpA) • Existing diagnosis of inflammatory arthritis • General Practice Clinician (GPC) deems unsuitable • Radiation of leg pain below the knee (i.e. neuralgia/sciatica) • Contraindications to MRI, e.g.: o Pacemaker o Ferrous metal in situ o Pregnancy (0- 12 months post-partum) o Claustrophobia • Suspected red flags • Cauda Equina Syndrome • Spinal Fracture • Cancer • Bone/disc infection

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Description of interventions	As part of this test accuracy study consented participants will complete participant reported outcome measures (PROMs) within a study questionnaire and receive a clinical assessment, x-ray, blood tests and MRI scan
Duration of study	Overall: October 2024- January 2027 Per participant: It is envisaged that a clinical diagnostic decision would be reached within 6 months of entering the study (and frequently a shorter period of time).
Randomisation and blinding	n/a
Statistical methods	The analysis and reporting of the study will be in accordance with STAndards for Reporting of Diagnostic Accuracy (STARD) and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + Artificial Intelligence (TRIPOD+AI) reporting guidelines.

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FLOWCHART

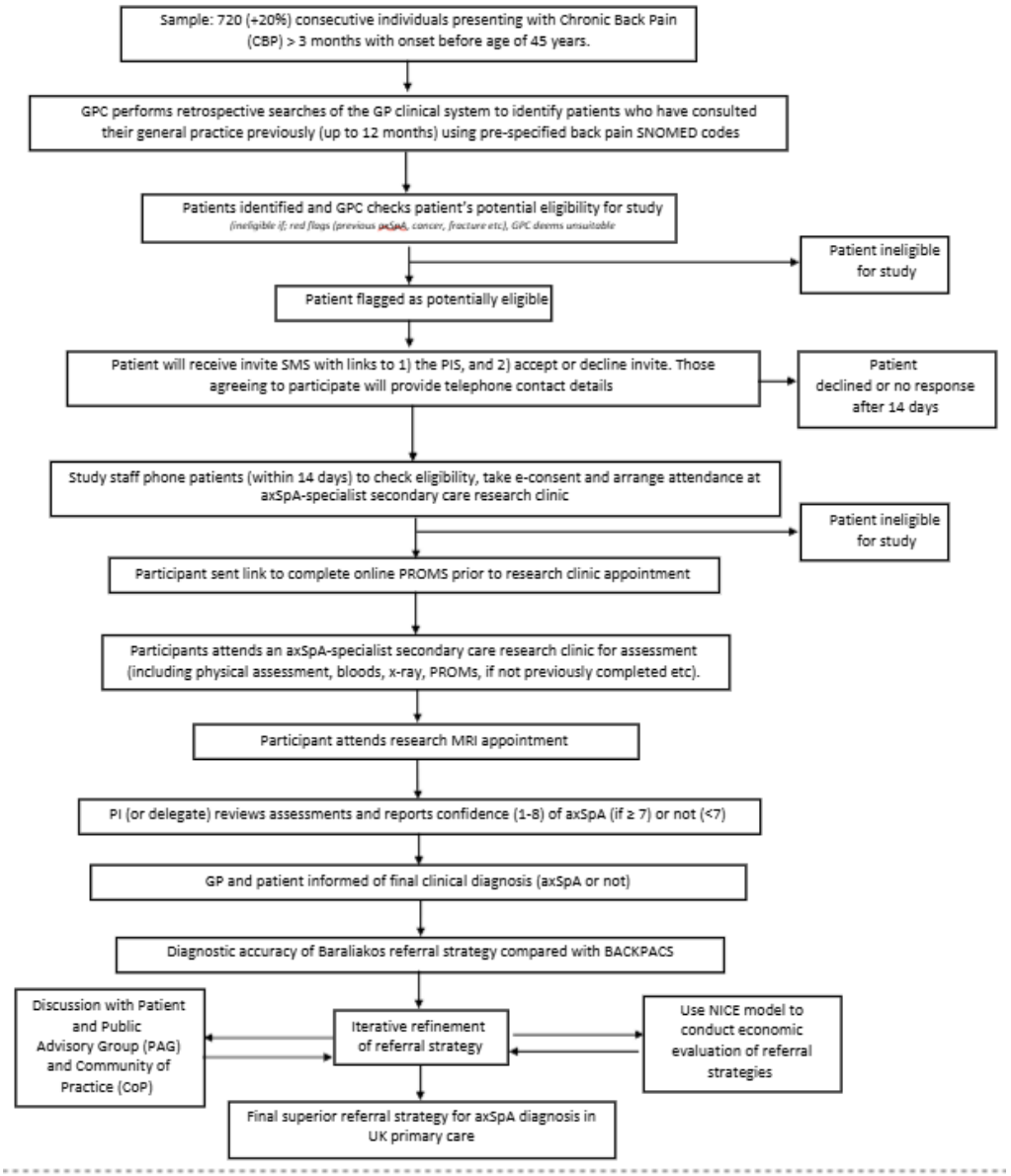


Figure 1: Flow chart outlining the study pathway. Abbreviations: Chronic Back Pain (CBP), General Practice Clinician (GPC), Systemized Nomenclature of Medicine (SNOMED), electronic health records (EHR), Participant Information Sheet (PIS), Short message service (SMS), Axial spondyloarthritis (axSpA), Patient Reported Outcome Measures (PROMs), Magnetic Resonance Imagining (MRI), BACK Pain referral pAthway from Community to Specialist care (BACKPACS), Patient and Public Advisory Group (PAG), Community of Practice (CoP), The National Institute for Health and Care Excellence (NICE).

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ABBREVIATIONS

Abbreviation	Term
APPG	All Party Parliamentary Group
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
AxSpA	Axial Spondyloarthritis
BACKPACS	BACK Pain referral pAthway from Community to Specialist care
CaFaSpA	Case Finding Axial SpondyloArthritis
CBP	Chronic Back Pain
CEAC	Cost Effectiveness Analysis Curves
CI	Chief Investigator
CoP	Community of Practice
CRF	Case Report Form
eCRF	Electronic Case Report Form
EHR	Electronic Health Records
GCP	Good Clinical Practice
GP	General Practitioner
GPC	General Practice Clinician
HLA-B27	Human leukocyte antigen-B27
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICER	Incremental Cost Effectiveness Ratio
IDEAL	Improving the Diagnosis and Early referral of patients with AxiaL spondyloarthritis
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MRI	Magnetic resonance imaging
NSAID	Non-Steroidal Anti-Inflammatory Drug
NASS	National Axial Spondyloarthritis Society
NCTU	Nottingham Clinical Trials Unit
NICE	The National Institute for Health and Care Excellence
NHS	National Health Service
PAG	Patient Advisory Group
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PMG	Programme Management Group
PPI	Patient and Public Involvement
PROMs	Patient Reported Outcome Measures
PSC	Programme Steering committee
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development

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REC	Research Ethics Committee
RDN	Research Delivery Network
SIJ	Sacroiliac joint
SOP	Standard Operating Procedure
SMS	Short Message Service
SNOMED	Systemized Nomenclature of Medicine
SSI	Site Specific Information
STARD	STAndards for Reporting of Diagnostic Accuracy
TMF	Trial Master File
TRIPOD+AI	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + Artificial Intelligence
WP	Work Package

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1.1 Background

Axial spondyloarthritis[1] (axSpA) is a common inflammatory rheumatic condition frequently starting in early adulthood, characterised by chronic back pain (CBP). AxSpA affects 1 in 200 adults, with 270,000 people in the UK living with this painful and progressive condition [2, 3]. It is a relatively recent rheumatological classification, developed by the Assessment of SpondyloArthritis international Society (ASAS) [4] which is now internationally accepted as the 'gold standard' and routinely used to aid clinical diagnosis. The previous diagnostic criteria for ankylosing spondylitis (AS) [5] required plain x-ray proof of damage to the sacroiliac joints (SIJ) at the base of the spine for diagnosis, which often takes many years to develop. These limitations led to development of the ASAS classification and a change in disease name from AS to axSpA. AxSpA includes a much wider spectrum of inflammatory spinal disease with potential to be detected earlier in disease course, particularly with magnetic resonance image (MRI) changes and clinical features enabling early diagnosis before the development of x-ray changes.

In adults, back pain is an extremely common symptom, responsible for up to 7 million GP consultations each year [6], with 700,000 having pain persisting over 12 weeks [7]. European primary care cohorts [8, 9] have shown that 14% of patients with more than 3 months of chronic back pain have axSpA if the onset of the back pain is before the age of 45. In most countries, patients with CBP are first seen by primary care health professionals. Guidelines with red and yellow flags are used to diagnose, treat and, if necessary, refer patients with CBP [10, 11]. These guidelines, which include the widely adopted STarT Back tool [12] developed at Keele University, do not screen for, or make any referral recommendation specific to axSpA. AxSpA diagnosis is frequently delayed, with an average time from symptom onset to diagnosis of 5-8 years [13-17] even with the newer ASAS classification criteria. This delay leaves people in pain and puts them at risk of developing irreversible damage, with long-term impacts on life and work [18-21]. AxSpA can be effectively treated [22-25], but only once the right diagnosis is made. Treatment is more effective if diagnosis is made early.

Because most CBP is due to non-inflammatory causes, identifying people likely to have axSpA is challenging, especially in non-specialist/primary care settings. Recognition of individual back pain symptoms as being relevant to a diagnosis of axSpA is highly variable amongst GPs (13-90%) [27]. There are knowledge gaps in differentiating mechanical from inflammatory back pain, in GPs being able to describe axSpA and a perception that axSpA is almost exclusively diagnosed in men [28] (whereas 50% of patients with axSpA are female) [29-31]. Self-management interventions (keeping active, analgesics) advised for mechanical back pain may partially improve axSpA symptoms, but these are unlikely to substantially prevent underlying disease progression or damage but could potentially delay diagnosis. There are inequalities in receiving a timely axSpA diagnosis, one secondary care European study [32] described a 2:1 male: female odds ratio of receiving an axSpA diagnosis and a UK ankylosing spondylitis (AS) study [17] reported both an increased delay to diagnosis for women and reduced likelihood of AS diagnosis with increasing social deprivation.

Referral strategies for axSpA aim to achieve earlier referral of patients suspected of having axSpA by primary care physicians. However, at the time of the 2018 NICE spondyloarthritis clinical guidelines, most of the published referral rules were either too complex to implement, costly, or had been developed in secondary care populations, making it hard to justify their introduction into primary care practice. There is a need to optimise early identification/referral of all people with potential symptoms/signs of axSpA to reduce unnecessary delay, resulting in earlier management and effective treatment.
As the IDEAL – BACKPACS study will look to develop a superior referral strategy for patients who potentially have axSpA by building on Baraliakos [9], we will identify any additional potentially predictive variables that may be relevant for prompt diagnosis of axSpA

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in a UK context by evaluating available data from existing UK axSpA cohorts (these cohorts have pre-existing ethical approval for this analysis).

Once we have determined if any additional variables are significantly associated with UK patients experiencing delay, in addition to those already outlined by Baraliakos et al, we will feed back this information to our Patient Advisory Group (PAG) and Community of Practise (CoP) partners. Through conversations between these groups and the study co-applicants we will refine the final set of variables to be collected as potential predictors of diagnostic delay (and subsequently modelled into a new referral strategy) in the current study (IDEAL – BACKPACS).

1.2 Study Rationale and Design Justification

Reducing axSpA diagnostic delay has become a central goal of many national institutions striving to improve healthcare for axSpA patients, including the National Institute for Health and Care Excellence (NICE) 2017 spondyloarthritis clinical guidelines [3] with clinical specialist advisors including Professor J Packham and Dr N Goodson. NICE state that "Commissioners should ensure that local arrangements are in place to coordinate care for people across primary and secondary (specialist) ensuring prompt access to specialist rheumatology care". Their top priority for research suggested "a single large, representative cohort study measuring the predictor variables for all reasonable referral strategies (which would) provide the ability to develop and validate any number of possible referral strategies. The study would need to be large enough that sufficient data are available to derive (and validate) new referral rules."

National Axial Spondyloarthritis Society (NASS) have developed a website 'Act on Axial SpA'[26] with Professor R Sengupta as a medical advisor. This website aims to reduce diagnostic delay in axSpA with the stated aim that, "It should be possible for every person experiencing symptoms of axSpA to receive a diagnosis within one year of symptom onset.". This website includes a patient self-screening tool which would benefit from an underlying evidence base.

The UK government axSpA All Party Parliamentary Group (APPG) 2020-22 [33] heard presentations and received advice from Professors Packham and Sengupta. The APPG stated that "Implementing a pathway for people with suspected axial SpA can not only reduce the time to diagnosis and streamline services, it can also have a positive economic impact, reducing societal and individual costs"

AxSpA can impact negatively upon many facets of a patient's life. A recent systematic review found that people with a delayed axSpA diagnosis had a greater likelihood of depression, work disability, poorer quality of life and higher health care costs. In addition, their disease had a significant societal impact, due to economic factors such as work disability [34, 36] and health care costs [18]. Between 10-40% of people leave employment due to their axSpA and individuals with axSpA retire 9.5 years earlier on average than the general population [37]. AxSpA is linked to both increased morbidity (e.g. stroke relative risk 1.5[38]) and mortality (hazard ratio 1.6[35]). Quality of life and work participation can be dramatically improved with effective treatments once a diagnosis is made, [22-25] although treatment response is less likely if diagnosis is delayed [20]. Reducing diagnostic delay would prevent patients living with pain for longer and reduce worsening outcomes across a wide spectrum of disease impact including disease activity [18-20], quality of life [18], fatigue [21], physical function [18, 19], spinal mobility [18, 19], mental health [18, 21] and radiographic spine damage [18, 19].

Health economic data [18] suggest that increased diagnostic delay is associated with personal economic disadvantage, with increasing risks of work disability/unemployment

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(cumulative 2.1% per annum) [39]. Three studies [18] report longer diagnostic delay is associated with higher healthcare costs (doctors' visits/specialist services/spinal surgery/treatments). One Italian study [40] estimated excess "unduly spent" national healthcare costs in the 3 years prior to axSpA diagnosis of €5.4 million.

A recent full economic cost evaluation commissioned by NASS modelled a prediction that the cumulative costs to an individual/employer with a diagnosis delayed by 8.5-year would be £186,479. The same model estimated a cost to the UK economy of axSpA delay of £18.7 billion (health care costs 3.6%, out of pocket costs 31.3% and productivity loss costs 56.1%) [41]. They state that if "axSpA patients were diagnosed after 1 year (rather than the current 8 years), this would save the UK economy £167.000 per person".

Crucial to reducing the delay to diagnosis of axSpA is early recognition in primary care of individuals with high likelihood of disease and subsequent referral to a rheumatologist for investigation and diagnosis, through a combination of clinical history/examination, x-rays, MRI scans and blood tests (inflammation and Human leukocyte antigen [HLA]-B27 genetic markers). Without widely adopted axSpA screening tools developed for use in primary care, it is challenging to determine the clinical or cost-effectiveness of screening for axSpA in general practice (or other clinical areas where patients might be identified).

At the time of publication of the 2017 NICE spondyloarthritis clinical guideline [3], most published referral strategies were complex, difficult to use, costly, or developed/validated in secondary care populations with poor evidence supporting primary care implementation. NICE's research recommendations included developing "optimal referral criteria for people with suspected axial spondyloarthritis" utilising UK data; no screening strategies had been evaluated solely in a prospective primary care cohort of CBP patients. A subsequent 2020 German referral strategy study [9] (mixed GP/community orthopaedic cohort) is promising but was underpowered and requires evaluation in a larger prospective UK primary care cohort.

NICE [3] pre-specified that a "positive likelihood ratio ≥ 2 would constitute significant diagnostic value" (… for an axSpA referral strategy). Excluding referral strategies that include x-ray/MRI imaging in the community (which are costly and potentially harmful) and those which rely solely on inflammatory back pain (IBP) (which have unacceptably low specificity)[2, 43], there are 4 existing published axSpA referral strategies; the Baraliakos [9], the Case Finding Axial SpondyloArthritis (CaFaSpA) referral strategy [15], the modified Braun strategy [45] and The 'Assessment of SpondyloArthritis international Society (ASAS) strategy [44]. See 3.1.3 Index tests for further information.

Three strategies [15, 44, 45] were retrospectively evaluated in the Dutch SPACE cohort [46], comprising 107 patients diagnosed with axSpA by a specialist, out of 261 patients already referred into rheumatology with back pain. The SPACE cohort [46] and a comparable evaluation of the fourth strategy (Baraliakos) [9] both used specialist rheumatologist clinical diagnosis as a reference standard (Table 1).

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Table 2 : Referral strategy performance

	Sensitivity	Specificity	Likelihood ratio
Braun 2-step	0.90	0.60	1.82
Modified Braun 2-step	0.86	0.73	2.10
CaFaSpA >1	0.94	0.31	1.25
CaFaSpA > 2	0.61	0.74	1.98
ASAS >1	1.00	0.16	1.82
Baraliakos	0.91	0.67	2.78

Only the modified Braun [45] strategy and the subsequent Baraliakos strategy [9] achieve a likelihood ratio >2. The modified Braun strategy [45] was suggested for use in the NICE spondyloarthritis clinical guideline [3], but this guideline predates the Baraliakos strategy [9] which has a higher likelihood ratio and is itself a simplification of the Braun strategy.

The Baraliakos strategy clearly has the potential to improve the supporting evidence base for incorporating an axSpA referral strategy into clinical practice. However, there are some aspects of this study that suggest that it needs independent validation and that it may not perform identically in the population it is intended to screen.

Firstly, the study recruited from both GP practices (30%) and community orthopaedic clinics (70%), so may reflect a slightly different healthcare system and population than might be encountered in a pure primary care setting. The study recruited from community clinics surrounding a single tertiary centre and was not multicentre, potentially limiting the evidence base for referral strategy roll out. Participants were 45 years of age or younger, so it does not provide an evidence base for individuals over 45. The ASAS classification criteria include patients having onset of back pain before 45 years (who with delayed diagnosis might well be over 45 years at the time of referral). There
are also some concerns that the Baraliakos paper modelled a large number of potential referral strategies, with no adjustment for multiple comparisons which might result in an overestimate of the benefits of the strategy [47]. The optimal Baraliakos strategy includes raised CRP, response to NSAIDs and HLA-B27 testing, which necessitate clinical follow up to assess whether individuals are positive for these variables. This additional potential burden on primary care clinicians may have a detrimental impact on the feasibility, acceptability, and consequent uptake of the Baraliakos referral strategy.

Therefore, although the Baraliakos strategy does appear to outperform Braun [45], it still requires validation in an independent prospective multicentre primary care cohort and an assessment of implementation feasibility in primary care. The data required to be collected to validate this strategy also provides an exciting opportunity to iteratively model a new alternative referral strategy, against which the existing Baraliakos strategy can be compared. This new strategy would have the potential to address many of the concerns mentioned above.

However, should the Baraliakos model prove superior, the development of an electronic pop up on GPs IT systems to inform referral from primary care, would help lower barriers to its use.

2. STUDY OBJECTIVES AND PURPOSE

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2.1 Purpose

The aim of this study is to determine the optimum referral strategy for the identification of axSpA.

2.2 Co-primary Objectives

1) Externally validate the Baraliakos strategy's predictive performance, including sensitivity, specificity, likelihood ratio, calibration and discrimination in a community-based population in the UK.

2) Model an alternative UK-specific axSpA referral strategy using combinations of existing Baraliakos predictors and any additional candidate predictors identified in the IDEAL programme evaluation of existing UK axSpA cohorts with pre-existing ethics.

2.3 Secondary Objectives

- Determine the most clinically effective ('superior') referral strategy by comparative analysis of the four pre-existing candidate strategies [the Baraliakos [9], modified Braun [45], ASAS [44] and CaFaSpA [15]) and the BACKPACS model. The study team anticipate that this will result in either the BACKPACS or Baraliakos strategy going forward as the 'pop up' in a separate implementation study, IDEAL-DIRECTED.

- To compare the acceptability and clinical effectiveness of the BACKPACS and Baraliakos referral strategy.

- Evaluate the NASS patient screening questionnaire to determine whether patient self-assessment prior has the potential to reduce delays in diagnosis.

- Estimate of prevalence of axSpA in UK primary care CBP population.

- Evaluate the individual potential screening variables.

- To assess the cost-effectiveness of different axSpA referral strategies, comparing strategies with current care and a comparison between strategies in a fully incremental analysis, applying the rules of simple and extended dominance.

3. STUDY DESIGN

3.1 Study configuration

3.1.1 Study Design

This study can be characterised as (a) a prospective diagnostic test accuracy study to externally validate the existing Baraliakos referral strategy, (b) a diagnostic modelling study to develop an alternative UK-specific strategy, and (c) a comparative test accuracy study to compare the performance of these and other referral strategies.

3.1.2 Reference standard

The primary reference standard will be clinical diagnosis by a rheumatologist reviewing all clinical and diagnostic parameters. Diagnostic confidence will be reported on an 8 point Likert scale as described in Table 3, with scores of 7 or 8 considered as diagnosed with

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axSpA. Reviewing rheumatologists will not be provided with any results from existing screening tools to inform the presence or absence of axSpA.

The reference standard for the primary analysis will be comprised of a confirmed diagnosis (a score of 7 or 8) versus normal or equivocal (a score from 1 to 6).

Table 3: Pre-defined reference standard for a diagnosis of axSpA

Diagnostic category	Score	Definition
Normal	1	axSpA definitely not present
Normal	2	axSpA not present
Equivocal	3	axSpA probably not present
Equivocal	4	axSpA possibly not present
Equivocal	5	axSpA possibly present
Equivocal	6	axSpA probably present
Diagnosed	7	axSpA present
Diagnosed	8	axSpA definitely present

The ASAS axSpA classification will be a secondary reference standard (Figure 2).

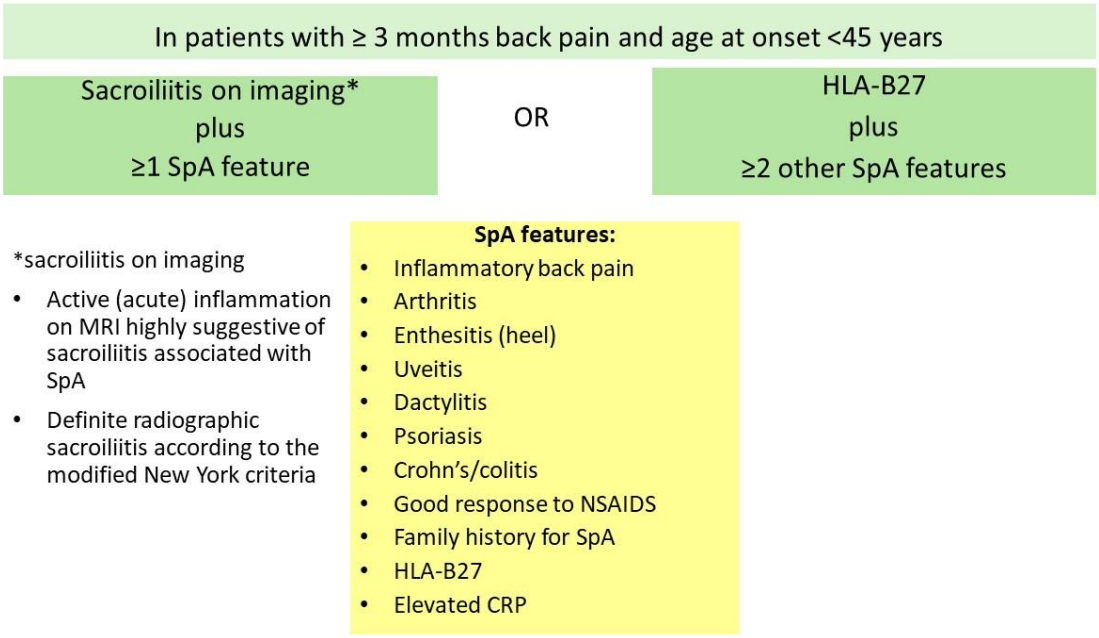


Figure 2: ASAS classification criteria for axial spondyloarthritis (axSpA)

3.1.3 Index tests

Index tests are the BACKPACS model (to be developed within this study) in addition to existing referral strategies described in

Table 4.

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Table 4: Index tests

Index tests	Assessment
The Baraliakos strategy [9]	Assesses 3 clinical variables. If 2 or 3 of these variables are present (or a 'second step' HLA-B27 test is positive) then secondary care referral is suggested: • improvement in pain with NSAIDs after 48 hours • raised CRP (blood test) • early morning stiffness (≥ 30minutes) This strategy requires follow up after the initial primary care clinic appointment.
The Modified Braun strategy [45]	Assesses 10 clinical variables and if at least 4 of these 10 variables are present then secondary care referral is suggested: • low back pain that started before the age of 35 years • waking during the second half of the night because of symptoms • buttock pain • improvement with movement • improvement with non-steroidal anti-inflammatory drugs (NSAIDs) • a first-degree relative with spondyloarthritis, • current/past arthritis, • current/past enthesitis • current/past psoriasis • HLA-B27 genetic test
The 'Assessment of SpondyloArthritis international Society (ASAS) strategy [44]	Patients with chronic backpain (≥ 3 months) with onset before 45 years, should be referred if at least one clinical variable is present: • Inflammatory backpain • HLA-B27 positive • Sacroiliitis on imaging, if available (x-ray or MRI) • Peripheral manifestations (arthritis, enthesitis and/or dactylitis) • Extra-articular manifestations (psoriasis, inflammatory bowel disease and/or uveitis) • Family history for spondyloarthritis • Good response to NSAIDS • Acute elevated phase reactants (c-reactive protein or erythrocyte sedimentation rate)
The CaFaSpA referral strategy[15]	Easy to use and was developed in a primary care setting but was not adopted by NICE spondyloarthritis clinical guideline[3], as the study cohort reported a much lower than expected prevalence of HLA-B27 positive individuals. The explanation for this may be related to the study having a lengthy retrospective recruitment time for individuals with CBP (median 10 years), whilst excluding patients diagnosed with axSpA during this

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	period; many of the excluded individuals with axSpA would have been HLA-B27 positive. This approach probably resulted in a substantial reduction in axSpA prevalence in this cohort, compared to that expected in real-life clinical practice.

3.2 Study Management

The roles and responsibilities for each organisation are documented in the Contractual Agreement and the responsibilities of the (Sponsor/CI/NCTU) specifically are detailed in the Delegation of Responsibilities agreement.

Chief Investigator
The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

Sponsor
University of Nottingham will undertake the role of Sponsor as defined by the UK Policy Framework for Health and Social Care Research 2017. Delegated responsibilities will be assigned to the Chief Investigator, participating NHS Trusts and Nottingham Clinical Trials Unit.

Trials Unit
The study is co-ordinated by the Nottingham Clinical Trials Unit (NCTU).

Programme Management Group
The Programme Management Group (PMG) will be responsible for the day-to-day management of the study. Membership includes (but is not limited to) the CI, Trial Manager, Trial Statistician and other members of the NCTU multidisciplinary team as appropriate. The PMG will ensure high quality study conduct, to time and within budget, monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself. The PMG will also be responsible for ensuring project milestones are achieved. The PMG will meet regularly during the entire course of the study.

Programme Steering Committee
A Programme Steering Committee (PSC) will be established which includes an independent chair, independent and non-independent members and patient representatives. The role of the PSC is to provide oversight of the study. A meeting will take place approximately 6 months then 18 months after the first participant is recruited with all meetings thereafter taking place approximately every six months during the recruitment phase of the study.

PSC members will be asked to sign the IDEAL PSC Charter which will outline their roles and responsibilities. The PSC will consider and act, as appropriate in accordance with the PSC Charter, and ultimately carries the responsibility for deciding whether the study needs to be stopped on the grounds of safety or efficacy.

Data Monitoring Committee
There will be no separate Data Monitoring Committee (DMC) formed for this project as no safety data is being collected. The PSC will act in accordance with the PSC charter and oversee the project as appropriate. If the need arises, the independent members of the PSC will have the opportunity perform the role of a DMC (for example, to review confidential data separately to the PMG).

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3.3 Duration of the study and Participant involvement

3.3.1 Study Duration

The study is planned to start in October 2024 with recruitment of participants for 15 months and data lock after 22 months.

Participant Duration: It is envisaged that a clinical diagnostic decision would be reached within 6 months of the participant entering the study (and frequently a shorter period of time).

3.3.2 End of the Study

This protocol relates to BACKPACS, which is work package 2 (WP2) of the IDEAL programme grant. The end of this study (WP2) will be the date of final database lock (when we reach a minimum of 720 participants), at which point the final analysis will be undertaken. NCTU will notify the REC when the IDEAL WP2 has ended, and a summary of the clinical study report will be provided within 12 months of the end of WP2. The remainder of the programme grant (WP 3 and 4) will continue and be covered by a separate protocol.

3.4. Selection and withdrawal of participants

3.4.1 Recruitment

Study Setting
Patients will be identified from General Practices (GP) acting as Patient Identification centres (PIC) and then clinically assessed at their local secondary care research centre site (all sited in rheumatology services with strong axSpA expertise). GP practices surrounding each research centre will identify patients presenting with CBP by Systemized Nomenclature of Medicine (SNOMED) code or prior identification as a back pain consultation. General Practice Clinicians (GPCs) responsible for evaluating patients with back pain will reflect the present clinical diversity of health professional expertise assessing this patient group and may include general practitioners, physician associates, first contact physiotherapists and practice nurses.

Participant Identification, screening, and recruitment
Participants may be approached by a variety of methods:

1) *Pop-up method*

Patient with back pain consults their general practice, dependent on the availability of staff at the GP practice, patients may be given a miniaturised copy of the study poster to prompt discussion during their consultation.

GPC enters ‘back pain’ SNOMED code, triggering patient eligibility screen template (pop-up) in electronic health record (EHR) if patient is aged between 16-50 years.

GPCs will assess for suspected red flag exclusion criteria in potential participants (see 3.4.2 Eligibility criteria). If a patient is potentially eligible and the GPC deems them suitable for the study, they will briefly introduce the study and ask the patient whether they would be willing to receive an SMS invitation to the study. The GPC will complete a simple and brief electronic pop-up to confirm the patient has current back pain and more than 3 consecutive months of chronic back pain in the last 12 months, absence of red flags and verbal agreement for an SMS invite to be sent. If the patient is not eligible, or not interested in being contacted about the study, the GPC will indicate this within the pop-up. If a potential

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participant fails screening, and then later presents with > 3 months back pain, they can be re-screened for eligibility at the GP primary care assessment stage.

If the patient agrees to be contacted, an SMS text message invite will be sent to them by the GP practice, containing a link for the online electronic Participant Information Sheet (ePIS), and a summary of the consent clauses which can be downloaded by the potential participant if they wish. Participant information will be provided in a variety of engageable formats (may include infographics, videos, and language translation). An additional link which will direct patients to the REDCap study database, will ask whether they accept or decline the invitation to be contacted to hear more about the study. Those who decline will be advised to contact their GP if their symptoms persist. Those who accept will provide information in the REDCap database to include (but not limited to), full name, date of birth, GP surgery, contact telephone number, email address and need for a video call (if hearing impaired). Site specific reports will be generated containing the personal contact details of interested patients, these will be accessed by a member of the research team to facilitate a research eligibility telephone call, or video call.

Regular reports may be generated within the GP systems containing information on patients approached and considered, and how many patients are deemed ineligible at the pop-up stage. These anonymous and aggregated reports will be shared with the coordinating centre as means of tracking screening/enrolment.

For patients that accept the invitation to join the study, a member of the research team will follow-up with a telephone call (or video call, if the patient requires this e.g. is deaf or hearing impaired) to confirm receipt of the study information, provide an additional verbal explanation of the study, answer any questions, and, if interested, confirm eligibility. Potential participants who are interested and confirmed eligible during the telephone call will be provided with a personal link to the online electronic Informed Consent Form (eICF) (see section 3.4.5), enabling them to review the requirements of the study and provide written informed consent (as detailed below).

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

For patients with poor IT/literacy skills we will develop animated videos describing the study to improve accessibility and recruitment for patients with first language other than English, and those underserved groups.

2) Retrospective search of electronic health record

Recruitment will be regularly assessed by the Programme Management Group (PMG), if recruitment is not sufficient using method 1, potentially eligible patients will be identified by a search/es of the GP clinical system for patients who have consulted with their GPC previously (up to 12 months) using pre-specified back pain SNOMED codes. Where available, SNOMED codes for exclusion criteria will be used to remove patients not eligible for the study. GPC clinical staff may then review the generated list of patients for anyone inappropriate to invite into the study. Patients previously contacted will be excluded from subsequent searches.

An SMS message will be sent to the identified list of patients to invite them to take part in the study. This will include a link to or copy of the PIS. They will also be provided with a link which will direct them to the REDCap study database and will ask whether they accept or

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decline the invitation to be contacted to hear more about the study. Patients that express an interest in the study will then follow the processes as described in method 1.

Managing patient flow from primary to secondary care
The pop-up can be switched on/off at any time, either through the local NIHR Research Delivery Network (RDN, formally known as Clinical Research Network; CRN) or GP practices. If needed, we will limit the number of active recruiting GPs we have at one time, to enable staggering of secondary care appointments. Current waiting lists at each trust involved in the study can vary. It is important that we do not overwhelm capacity within the research clinics to ensure that patients referred into the study by their general practice are seen and assessed in a timely fashion.

Posters advertising the study may be displayed in participating GP practices.

3.4.2 Eligibility criteria

Inclusion criteria
- Aged 16-50 years with onset of chronic back (cervical/thoracic/lumbar) pain before 45 years.
- Current back pain and at least 3 consecutive months of chronic back pain in the last 12 months.
- Ability to provide written/electronic informed consent.
- Willingness and ability to undergo all study assessments (i.e. clinical examination, X-ray, MRI, blood sample collection).

Exclusion criteria
- Existing diagnosis of axSpA.
- Existing diagnosis of inflammatory arthritis.
- GPC deems unsuitable.
- Radiation of leg pain below the knee (i.e. neuralgia/sciatica)
- Contraindications to MRI, e.g.:
    - Pacemaker
    - Other ferrous metal in situ
    - Pregnancy (0-12 months post-partum)
    - Claustrophobia

Suspected red flags in the history or clinical examination that may indicate further investigation or referral for possible serious underlying pathology:
- Cauda Equina Syndrome
- Spinal Fracture
- Cancer
- Bone/disc infection

3.4.3 Expected duration of participant participation

Study participants will be participating in the study until a clinical decision on diagnosis has been made. This is expected to be a maximum of 6 months (and frequently a shorter period of time).

3.4.4 Removal of participants from therapy or assessments/Participant Withdrawal

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Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participants may withdraw their consent for follow-up and other study-related activities including receiving study related communications. The NCTU must be informed of all requests by participants to stop their involvement in the study; appropriate action will be taken to ensure that the participant's wishes are followed.

Sites will be trained to determine which activities participants may wish to withdraw from.

Withdrawal type	**Withdrawal procedure**	**Use of data**
Discontinue from study communications	Any participant who requests to be withdrawn from other study communications will be removed from all mailing lists for ongoing study contact (e.g. newsletters and reminders).	N/A withdrawal from communications only.
Collection of data from medical records and/or NHS Digital	Any participant that requests to discontinue collection of routine data will be directed to the national data opt out service.	Any data collected prior to participant withdrawal will be retained and used.
Full study withdrawal	Any participant that requests to have no further involvement in the study will be marked as withdrawn on the study database.	Any data collected prior to participant withdrawal will be retained and used in the analysis as described in the PIS.

If site staff are made aware of a participant's discontinuation from any study activities, the PI or delegate should record this in the eCRF as soon as possible to ensure the correct procedures are followed by the coordinating centre and the site team. Participants will be asked their reason(s) for withdrawal but are not obliged to provide these.

Withdrawn participants will not be replaced. Data collected prior to withdrawal will be retained and used in the analysis as described in the PIS.

3.4.5 Informed consent

Consent Forms in IDEAL-BACKPACS	**Method (e-consent or face-to-face)**	**Person taking consent (PI, RN, PI or delegate, etc)**	Use of legal representatives (Y/N)
Main Study	e-consent	PI, RN or delegate	N
Optional Consents (completed under separate study with separate ethical and HRA approval)			

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Biomarkers (blood) and diagnosis data sharing	face-to-face	PI, RN or delegate	N

Informed e-consent for each participant must be obtained and documented (using the online electronic informed consent form) prior to performing any study related procedure / PROM collection.

It remains the responsibility of the Principal Investigator (or appropriately trained delegate) to ensure informed e-consent is obtained appropriately**.** An electronic (or paper) Participant Information Sheet (ePIS) will be provided to facilitate this process.

Documentation of consent

After the initial general practice consultation, ideally within 2-3 weeks, potential participants, who have accepted the invite to the study, will receive a telephone, or video, call from a member of the research team. The research team will determine whether the potential participant wishes to enter the study and seek informed e-consent having re-checked eligibility criteria (and suspected red flags) and arrange assessment at the secondary care centre.

The potential participant will be given the opportunity to ask questions throughout the process and sufficient time to consider participating or not. Investigators or delegate(s) will ensure that they adequately explain the aim, anticipated benefits, and potential hazards of taking part in the study to the participant. They will stress that participation is voluntary and so the potential participant is free to decline participation and may withdraw from the study at any time.

If the potential participant expresses an interest in participating in the study, they will be asked to provide written consent using the latest version of the online electronic Informed Consent Form (eICF). Participants will be asked to complete the eICF and write their full name before submitting the online form; the date will be system-generated. The name of the investigator or delegate who provided the study information and the date the eICF was generated will also be recorded within the online system.

The eICF will be retained within the study database. Printable copies will be generated and retained within the Investigator Site File (ISF) and a copy will be made available electronically to the participant. Once the participant is entered into the study, the participant's unique study identification number will be entered on the Informed Consent Form maintained in the ISF.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include a statement that identifies that the participant is taking part in a clinical study and the name of the study as a minimum.

Subject to prior consent from the participants, once the participant completes the informed consent form the GP will be notified to let them know the patient has consented to the study and asked to record this in their medical notes.

The eICF will include a full audit trail documenting the date and time of information receipt and provision of written informed consent. It will also be necessary for written consent to be

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fully documented before the system will permit access to the online baseline data collection system.

Throughout the study the participant will have the opportunity to ask questions about the study. Any new information that may be relevant to the participant's continued participation, for example changes to the protocol or study procedures which impact on participants, will be provided through updates to the ePIS which will be notified to participants through text and/or email. Where new information becomes available which may affect the participant's decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented through electronic signatures obtained in an updated version of the eICF. The participant's right to withdraw from the study will remain.

Consenting individuals will be booked to a clinic appointment at their local secondary care research centre and will be sent a link to complete online study questionnaire.

If a potential patient declines or is not responsive to the SMS text message within 14 days of receipt, it will be the patient's responsibility to go back to the GP if their symptoms persist.

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

During the clinic appointment participants will have the option to consent and take part in an additional separate study, to determine which serological or genetic factors predispose to the development of axSpA. This additional study has existing ethical and HRA approval as part of the National biobank repository and is not covered in this protocol (approved by North West 5 – Haydock Park Research Ethics Committee, reference 99/8/084). Participation would involve consent to take an additional blood sample to be transferred, stored and processed at the University of Manchester and/or King's College, London for biomarker processing (to be covered by a material and data transfer agreement). Consent will be captured on a paper consent form. Where consent for participation in this additional study is given, axSpA diagnosis data from the IDEAL-BACKPACS study will be shared with the University of Manchester and King's College London. This will be shared in a pseudonymised format, and no patient identifiable information will be shared from the IDEAL-BACKPACS study teams. The consent form and/or the blood sample will be labelled with the IDEAL-BACKPACS study ID to allow linkage between the blood sample and the IDEAL-BACKPACS study data. University of Manchester may separately collect patient identifiable information as covered by their ethics approval. Participants will be asked to consent to this data sharing on the national biobank repository consent form. NCTU will hold a copy of this consent form to provide evidence of consent for data sharing and record consent on the trial REDCap database. If the participant declines to participate in this additional study, their participation in the IDEAL-BACKPACS study would not be affected.

Optional consent (on the main study informed consent form) will be sought for imaging data collected as part of the BACKPACS study, (x-ray and MRI images, in pseudonymised form) and stored in the University College London XNAT database, to effectively be included as part of an imaging biobank. This would be used for future appropriately approved research projects, which may be carried out by researchers other than the current team. If the participant declines this, they will continue their participation in the main IDEAL-BACKPACS study.

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4. STUDY REGIMEN

Table 5: Summary of assessments for the study

	STUDY PERIOD					
Timepoint	**Invitation and Screening**	**Eligibility and Enrolment**	**Consent and questionnaire**	**Secondary care assessment**	**Research MRI appointment**	**PI assessment and reporting**
Initial eligibility screen	X					
Contact details obtained	X					
SMS text invitation	X					
Agreement to participate		X				
Confirm eligibility		X				
Participant enrolment		X				
Written informed consent			X			
PROMS completion			X	X*		
Clinical assessment				X		
Blood sample (diagnostic test)				X		
X-Ray				X		
MRI					X	
Outcomes reported						X

*If not completed at previous timepoint, Participant Reported Outcome Measures (PROMs) can be completed as part of secondary care assessment.

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4.1 Schedule of assessments

4.1.1 Invitation and screening

For the pop-up method of recruitment, initial eligibility to approach is confirmed by the GPC during the primary care attendance. Patients aged 16-50 years who present with chronic back pain (with onset before 45 years) and do not present with any suspected red flags (as described in section 3.4.2 Eligibility criteria) will be approached. Basic screening information obtained from the consultation will be recorded on the pop-up.

For recruitment using retrospective searches, potentially eligible patients will be identified through searches of the GP clinical system using pre-specified back pain SNOMED codes. These searches will include patients who have consulted with their GPC within the previous 12 months. Where available, SNOMED codes relating to the exclusion criteria will automatically remove patients who are not eligible for the study. The resulting patient list may subsequently be reviewed by GPC clinical staff to exclude any individuals considered inappropriate to invite to participate, e.g. patients with suspected red flags.

4.1.2 Eligibility and enrolment

Following identification through either the pop-up or retrospective search (see section 3.4.1 Recruitment), an SMS text message will be sent from the GP surgery, with assistance from the RDN where appropriate.

The SMS text message will include a link for the electronic Participant Information Sheet, a summary of the consent clauses, and a link to accept or decline the invitation. Translated versions of the Participant Information Sheet may be available for those who do not have English as their primary reading language, as well as videos for those with limited literacy skills.

A member of the research team will telephone, or video call the potential participant to discuss the study in more detail, ensure thorough understanding of the study requirements and confirm eligibility.

4.1.3 Consent and PROMS questionnaires

Informed consent is received from patients using the online eICF. Consenting individuals will be booked for a clinic appointment at their local secondary care research centre clinic and will be sent a REDCap database link to complete an online questionnaire prior to their appointment. Up to 3 reminder emails and / or SMS texts may be sent to participants who have not completed their questionnaire.

The questionnaire will include Patient Reported Outcome Measure (PROM) questionnaires as described in Table 6 . The questionnaire will be completed online and take around 25 minutes to complete (on a single occasion). The questionnaire will include demographics, brief questions about inflammatory back pain (IBP) symptoms and clinical features (psoriasis and NSAID response), to allow evaluation of whether patient completed screening might contribute towards being an effective screening strategy.

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Table 6 Patient Reported Outcome Measures (PROMs)

Variable	Measure	Score
Spinal Pain	Numerical rating scale	0 (no pain) -10 (worst pain)
Fatigue	Functional Assessment of Chronic Illness Therapy (FACIT)[56] (and/or) Warwick Axial Spondyloarthritis Tiredness and Energy scale (WASTEd) [57]	FACIT WASTEd Fatigue 0-10 Energy 0-8
Disease activity	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Each question is scored on a scale of 0 -10, 0 indicates none and 10 indicates very severe. For the last question, 0 is 0 hours, 5 is one hour and 10 is two or more hours.
Physical function	Bath Ankylosing Spondylitis Disease Activity Function Index (BASFI) [60]	Each question is scored on a scale of 0-10. 0 indicates easy and 10 indicates impossible.
Fibromyalgia	ACR brief criteria [61]	Widespread pain index (0-19)
Quality of life	Evaluation of ankylosing spondylitis quality of life (EASiQoL)[50]	20 questions across the 4 domains of physical function, disease activity, emotional wellbeing and social participation. Each question is scored 0 (no limitation) to 4 (extreme limitation)
NASS self-referral criteria	Back pain onset before aged 40 Insidious onset (i.e. did you bend over and hurt your back) Duration > 3 months Early morning stiffness > 3 months Improves with movement Does not improve with rest Alternating buttock pain Wakes in second half of the night	Yes/no
Physical activity	International physical activity questionnaire and/or General practice physical activity questionnaire	Set of questions on the type and amount (in hours) of physical activity at work and at home.
Work productivity	Work Productivity and Activity Impairment Questionnaire (WPAI): General Health	Measures absenteeism, presenteeism, work productivity and activity impairment
Depression	PROMIS - Depression – Short Form 4a	Each item on the measure is rated on a 5-point scale from

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		1 indicating never, to 5 indicating always.
Anxiety	PROMIS - Anxiety – Short Form 4a	Each item on the measure is rated on a 5-point scale from 1 indicating never, to 5 indicating always.

4.1.4 Secondary care assessment

All participants will be seen in specialist rheumatology research clinics. If the participant does not attend their scheduled appointment they will be contacted by email, text and/or telephone to reschedule. If the participant is still unresponsive after up to 3 attempts to contact then the GP will be informed of their withdrawal from the study.

The secondary care assessment will consist of:

- Clinical assessment
- Blood sample collection
- X-ray
- Research MRI scan (likely to be a separate appointment)

On arrival at the local secondary care research clinic, if participants have not completed the study questionnaire electronically, they will be asked to do so as part of their consultation. There may be an option to complete a paper version of the questionnaire.

At the clinic appointment, an appropriately trained member of the clinical team will perform the semi-structured clinical research assessment (30 minutes for clinical assessment and 30-60 minutes for bloods and x-ray), evaluating axSpA features, using a standardised proforma listed in Table 7.

Participants will be asked if they have had a spinal/SIJ MRI scan in the last 12 months, if this is the case then the participant's previous MRI result will be assessed alongside the results of the research MRI scan.

Table 7: axSpA features evaluated in secondary care clinical assessment

axSpA feature	Method of assessment	Definition
Clinical assessment		
Peripheral arthritis	66/68 peripheral joint assessment	66/68-Swollen and Tender Joint Counts (SJC66/TJC68) Joints assessed include temporomandibular joint, (0-2) Sternoclavicular joint (0-2), Acromioclavicular joints (0-2), Glenohumeral(s) (0-2), Elbow(s) (0-2), Wrist(s) (0-2), Metacarpal phalangeal joints (0-10), Finger Proximal interphalangeal joint (0-10), hip(s) (tender score only 0-2), knee(s) (0-2), ankle(s) (0-2) ,

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		Tarsus/Midfoot (feet) (0-2), metatarsal phalangeal joints (0-10), toe PIP(s) (0-10) The joint count is scored as a sum of the swollen joints (0-66) and the sum of the tender joints (0-68)
	Dactylitis count	Past or present dactylitis diagnosed by a physician (categorised as present/absent) with current dactylitis count 0-20 ref
	Heel enthesitis	Presence of Achilles Tendonitis and/or Plantar Fasciitis
	Enthesitis	Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index and Leeds Enthesitis Index (LEI) 16 sites assessed in total: the greater trochanter, quadriceps tendon insertion into the patella, patellar ligament insertion into the patella and tibial tuberosity, Achilles tendon insertion, plantar fascia insertion, medial and lateral epicondyles, and the supraspinatus insertion. Presence or absence of tenderness; max score = 16
Mobility	Bath Ankylosing Spondylitis Metrology Index (BASMI)	Index comprising 5 measures of spinal and hip mobility
Personal history	a. Onset of chronic back pain symptoms b. Dactylitis c. Enthesitis d. Skin/nail psoriasis, e. Colitis f. Uveitis g. Anterior chest pain	Self-reported, current and previous
Family history	Presence in first degree or second-degree relatives* of any of the following: a. Skin/nail psoriasis b. Colitis c. Uveitis, d. axSpA, e. Reactive arthritis, f. PsA	Self-reported (yes/no) and number of relatives affected

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Response to NSAIDs	**Only** if NSAID response is not completely clear. At least one week at max tolerated dose. (If NSAID response if not completely clear) for individuals with no contraindications, min 7-day course of full dose NSAIDs (with telephone evaluation of NSAID response from research team at 1 week)	Self-reported (yes/no)
Blood tests		
Diagnostic laboratory tests	HLA-B27	Positive testing according to standard laboratory techniques.
	CRP	C-reactive protein above upper normal limit in the presence of back pain, after exclusion of other causes for elevated CRP concentration.
Imaging		
x-ray	Conventional SIJ plain x-rays	Modified New York criteria for each SIJ
MRI	SIJ and whole spine (30 min scan) arranged within 4 weeks** of clinical assessment.	(i) Description of oedema and structural features (fat metaplasia, erosions, ankylosis) in SIJs – yes/no for each. Interpretation according to ASAS specifications (bone marrow oedema in typical location 'highly suggestive' of axSpA) - yes/no for MRI positivity (ii) Are there unequivocal features of spinal inflammation? (yes/no) (iii) Overall impression across x-ray and MRI – (a) normal (b) equivocal (c) axSpA (d) other

*First degree relative includes an individual's parents, siblings and children. Second degree relative includes grandparent, grandchild, half siblings, aunt/uncle and niece/nephew. **where possible, waiting times may vary between sites.

4.1.5 Research MRI appointment

An appointment will be made for participants to attend a separate radiography appointment for a research MRI (it may be possible for the research MRI to be on the same day as the clinical assessment, bloods and x-ray). Appointment dates will be entered to the study

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database by the research team. Where possible, appointment reminders will be sent to participants (by the research team or the coordinating centre) including a request for the participant to notify the study team of any changes since their previous appointment e.g. if the participant has fallen pregnant within that time.

Participants will be asked to stop taking NSAIDs for one week before the MRI scan, they will be asked to take other medication, such as paracetamol instead, if necessary. NSAIDs can reduce bone marrow oedema on MRI so make it more difficult to detect signs of axSpA. Stopping NSAIDs may increase the diagnostic sensitivity. NSAID cessation for 1 or 2 weeks is now routine practice in the NHS prior to MRIs for suspected axSpA.

The participant will attend the research MRI scan and the SIJ and whole spine scanned. MRI techniques will follow the ASAS specifications [64] (see 3.1.2 Reference standard Appendix 1: Specification of the variables used for the ASAS-Criteria for classification of Axial Spondylarthritis) for identification of inflammatory bone marrow oedema and structural changes (erosions, sclerosis or ankylosis). See 4.2 Study Procedures for further information.

If the participant does not attend the initial scheduled MRI appointment, then they will be contacted to reschedule the appointment. If they continue to be unresponsive after up to 3 attempts to contact, no further attempts will be made and they will be withdrawn from the study.

Radiographs and MRIs will be read locally for safety, to exclude urgent conditions such as unexpected malignancy. Any unexpected results (including red flags) will be communicated urgently to the GP via letter (and an additional telephone call if clinically indicated) from the local PI (or delegate) so they can proceed with participant's care as appropriate.

X-rays and MRIs will also be centrally reviewed by at least two experienced musculoskeletal radiologists blinded to participants' clinical and laboratory data. The imaging reports will be uploaded to the study database.

4.1.6 PI assessment and reporting

The laboratory results, clinical assessment, x-rays and MRI reports will be sent to the local PI. The local PI (or delegate) will then review all clinical and diagnostic parameters. Diagnostic confidence will be reported on an 8 point Likert scale as described in Table 2 (Section 3.2), with scores of 7 or 8 considered as diagnosed with axSpA. Reviewing rheumatologists will not be provided with any results from existing screening tools to inform the presence or absence of axSpA. The ASAS axSpA classification [1] (see 3.1.2 Reference standard) will be a secondary reference standard.

The participant will be informed by the local PI (or delegate) whether or not they are likely to have axSpA or whether their back pain is likely to be due to non-inflammatory causes. A summary of the laboratory, x-ray and MRI reports will be forwarded to the participant's GP. The participant will also receive publicly available advice leaflets/website links, related to their diagnosis from the research site team.

If axSpA diagnosis is unclear, then it will be flagged to the GP in this letter. For patients with an equivocal likelihood of axSpA, further clinical investigation might be required in the future time in either primary or secondary care (at the discretion of the patient's primary care team).

All reports will be entered to the study database by site clinicians, or their delegates. This will include any diagnostics of serious conditions.

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4.2 Study Procedures

4.2.1 Blood sampling

Blood will be collected and processed as per local hospital laboratory standard operating procedures. The blood samples will be tested for the presence of HLA-B27 and CRP level. The samples will then be destroyed.

Where additional, and optional consent has been provided, additional blood samples will be collected and stored for biomarker analysis, which will be covered by separate ethics and HRA approval.

4.2.2 Imaging

Radiographs
For participants aged 18 and over, conventional SIJ plain x-rays will be taken.

MRI
MRI scans will be acquired according to a dedicated imaging protocol. Participants will have an MRI scan of their SIJ and whole spine (30 min scan) arranged within 4 weeks (where possible) of clinical assessment. For some secondary care sites, the MRI scan may be on the same day as the clinical assessment, if there is capacity. MRI scans will be acquired according to a dedicated imaging protocol which will be provided separately.

Briefly, SIJ MRI acquisitions will be performed in modified coronal plane (aligned with the long axis of the SIJ), using small field-of-view imaging and consistent resolution (matrix size) between the acquisitions.

We will acquire:

- T2-weighted STIR or turbo STIR imaging
- T1-weighted turbo spin echo imaging a
- T2-weighted Dixon turbo spin echo imaging (repeated with two effective echo times).

For the spine imaging, we will cover the whole spine in the sagittal plane, using either two or three blocks, using (i) T2-weighted STIR or 'turbo' STIR imaging and (ii) T1-weighted turbo spin echo imaging.

Data upload
Image data will be acquired in DICOM format and pseudo-anonymised by individual sites, before being uploaded to the XNAT platform for image storage and curation. Each site will have their own folder on the XNAT platform to minimise the risk of data leaks between sites.

Scan interpretation
All scans will be read by two consultant radiologists on the XNAT platform. If discrepancies exist regarding the overall impression of whether axSpA is present (i.e. whether the patient is 'imaging positive') across the MRI and x-ray, a third consultant radiologist will perform an additional read and make a final decision on the appropriate category.

The following will be included in the x-ray report:

- Modified New York criteria grade 0-4 for each SIJ.

The following will be included in the MRI report:

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- Description of oedema and structural features (fat metaplasia, erosions, ankylosis) in SIJs – yes/no for each.
- Interpretation according to ASAS specifications (bone marrow oedema in typical location 'highly suggestive' of axSpA) - yes/no for MRI positivity
- Are there unequivocal features of spinal inflammation? yes/no

The following will be included as an overall interpretation across MRI and x-ray:
(a) normal (b) equivocal (c) axSpA (d) other

ASAS specifications (bone marrow oedema and structural changes)

4.2.3 Post Study Care

Once the participant has completed all study assessments they will receive a letter with their diagnosis and publicly available advice leaflets/website links from the local PI (or delegate).

Participants identified as having axSpA will be followed up (outside of this research study) in standard NHS Rheumatology outpatient clinics.

Participants without axSpA will be provided with self-management advice and could seek further support from their GP.

In addition to a clinical research evaluation of each participant's MRI scan (which might occur some weeks after performed), a local standard NHS report of each MRI will be performed, by the radiology team where the MRI scan has taken place, and sent to the local PI at each research site. These reports will be available in the same time frame as a standard NHS non-research MRI report. These local reports will act as a safety measure, so that in the rare instance of an unexpected serious (non-inflammatory) pathology, such as malignancy, vertebral collapse or infection, causing the participant's symptoms, this pathology would be identified. The local PI would then communicate these findings to the participant's GP to ensure appropriate intervention and treatment occurs.

4.2.4 Compliance

The study analysis requires 720 participants with a complete screening dataset. We aim to recruit a total of up to 900 participants to allow for up 20% of participants not completing all study procedures. Compliance with study procedures will be monitored via data entered into the study database. Only those with a complete screening dataset will be included in the analysis.

4.2.5 Criteria for terminating study

There are no set criteria for terminating the study and an interim analysis is not planned. The study will be monitored by the programme management group and programme steering committee, who will receive regular progress updates. The PMG and PSC will only consider termination of the study if major insurmountable issues are identified.

4.5. Radiation exposure

4.5.1 Details of diagnostic or therapeutic ionising radiation

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For participants aged 18 and over, conventional SIJ plain x-rays will be taken.

Procedure	No of procedures	Estimated procedure dose
x-ray of pelvis/SIJ	1	4mGy/2.2 Gy/Cm2

4.5.2 Clinical Assessment

We estimate that 70% of participants would eventually be investigated for axSpA therefore additional ionising radiation exposure relates to 30% of our cohort. The exposure will not exceed the exposure that might be received as part of normal care at any proposed research site.

4.6 Collection, Storage and Analysis of Clinical Blood Samples (HLA-B27 / CRP)

The blood samples will be tested for the presence of HLA-B27 and CRP level. Collection, storage and analysis of clinical blood samples will be in line with local secondary care laboratories standard operating procedures. Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures. Samples will not be retained at the end of the study and will be destroyed in accordance with the Human Tissue Act, 2004.

It is the responsibility of the study site to ensure that samples are appropriately labelled in accordance with the study procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

5. STATISTICS

5.1 Methods

The analysis and reporting of the study will be in accordance with STAndards for Reporting of Diagnostic Accuracy (STARD) and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + Artificial Intelligence (TRIPOD+AI) reporting guidelines. A full statistical analysis plan (SAP) will be developed and agreed prior to database lock.

Descriptive statistics will be used to describe baseline characteristics, prevalence of axSpA symptom duration, pain severity and other clinical factors.

For each of the index tests (described in section 3.3) sensitivity, specificity, positive and negative predictive values, and likelihood ratios (and associated 95% confidence intervals) will be calculated to assess diagnostic accuracy and clinical utility, along with the area under the (receiver-operator characteristic) curve and calibration. Estimates of comparative accuracy between models will be obtained using appropriate statistical models and reported with 95% confidence intervals. Where necessary we will recalibrate models to allow for a difference in prevalence of disease in our population.

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To develop the BACKPACS strategy we will pre-specify 12 key variables to include in the initial modelling, although we would seek to develop models with 3 or 4 variables which would be most suitable for clinical use. Internal validation using 200 bootstrap samples and shrinkage will correct for overfitting. A prediction model equation or simplified clinical score will be presented in a user-friendly format, with performance summarised using discrimination (c-index) and calibration (plot in quartile risk groups) outcomes and graphs. Based on estimates of sensitivity and specificity, we will determine a sensible cut-off value above which patients could be referred to a rheumatologist.

Analyses will be conducted in Stata 18.0 or later.

Planned Subgroup Analyses

Where feasible, subgroup analyses will be employed to assess whether there are differences in accuracy of the referral strategies for the following groups:

- Age of symptomatic onset before 35 years vs. onset after 35 years
- Males/Females
- Caucasian vs non-Caucasian (related to variations in disease incidence with race)

5.2 Sample size and justification

The prevalence of axSpA is predicted to be similar to the 14.1% prevalence reported in the Baraliakos study [9]. Assuming a 14% axSpA prevalence, and a Baraliakos referral strategy with sensitivity 90% and specificity 65%, 720 patients will provide over 90% power to detect lower bounds of sensitivity 79% and specificity 58%. Allowing for 20% participants without full data (either due to non-attendance at clinic visits or uncertainty in estimates of prevalence/test accuracy), we aim to recruit up to 900 patients. Once 720 participants complete follow up and are fully assessable for clinical diagnosis of axSpA, recruitment will cease. This is due to the high costs of additional clinical review/MRI scans.

This sample size is sufficiently powered for the development of a model based on 12 variables with 0.8 c-index and allowing for 10% shrinkage to correct for overfitting.

5.3 Procedures for missing, unused and spurious data

The primary analysis will include participants who have provided complete data (i.e. for whom the index test and reference standard can be determined). The sensitivity of the findings to different assumptions about missing data will be explored through sensitivity analyses, which will be fully specified in the Statistical Analysis Plan (SAP).

5.4 Definition of populations analysed

The primary analysis will be conducted for participants who have provided complete data. Sensitivity analyses (fully specified in the SAP) will include all participants..

6. HEALTH ECONOMICS

Aim

The objective of the health economics analysis is to assess the cost-effectiveness of different axSpA referral strategies, comparing strategies with current care and a comparison between strategies in a fully incremental analysis, applying the rules of simple and extended dominance. A cost-utility analysis will be undertaken to calculate cost per quality-adjusted life

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year (QALY) gained from an NHS perspective. NICE thresholds of £20,000/QALY and £30,000/QALY will be applied to the results.

Outcome measurement
The cost-effectiveness analysis will use pre-existing equations, as developed and advised by NICE 2017 clinical guideline for spondyloarthritis. This is specified in the section outlining the analysis approach. Outcome data required for the equations for each referral strategy will be available from WP2, namely the prevalence of the condition and test sensitivity and specificity. Data on quality of life is not required as this has already been factored into the model equations using utilities for health states.

Resource Use Measurement
Data on the health care resource use required for each referral strategy will be collected during WP2 (e.g., tests administered, or extra appointments required) costs calculated using standard NHS unit costs.

Analysis
As part of the development of latest NICE clinical guidelines in axSpA, a detailed model-based economic evaluation of axSpA referral strategies was constructed [3]. The Markov model, with a 3-month time cycle and lifetime time horizon estimated the costs and utility of being correctly identified with axSpA and being misdiagnosed and therefore being treated for chronic low back pain of unknown cause. The evaluation of a superior referral strategy included a complex interaction of the benefits, costs and harms associated with false-positive and false-negative diagnoses, with potential approaches trading off sensitivity and specificity. A key output of the model is two equations, one for discounted costs and one for discounted QALYs to allow assessment of the cost-effectiveness of future referral strategies, without researchers having to reconstruct the decision model. We therefore propose to use these equations in our analysis.

The equations are:
Costs = $\boldsymbol{C} + \boldsymbol{vn}107{,}307 + \boldsymbol{v}(1-\boldsymbol{n})104{,}966 + (1-\boldsymbol{v})(1-\boldsymbol{p})559$

QALYs= $\boldsymbol{vn}14.571 + \boldsymbol{v}(1-\boldsymbol{n})13.534$

Where $\boldsymbol{C}$ is the initial cost of the strategy, $\boldsymbol{v}$ is the true prevalence of axSpA among people with chronic back pain of ≥3 months' duration with age of onset ≤45, $\boldsymbol{n}$ is the sensitivity of the strategy and $\boldsymbol{p}$ is the specificity of the strategy.

The equation for the incremental cost-effectiveness ratio (ICER) versus current care (as specified in the NICE guidelines) is as follows:

$$\text{ICER} = \frac{\boldsymbol{C} + \boldsymbol{vn}107{,}307 + \boldsymbol{v}(1-\boldsymbol{n})104{,}966 + (1-\boldsymbol{v})(1-\boldsymbol{p})559 - 5{,}264}{\boldsymbol{vn}14.571 + \boldsymbol{v}(1-\boldsymbol{n})13.534 - 0.682}$$

The strategies for comparison will be the validated Baraliakos strategy, the alternative UK referral strategy (BACKPACS) and existing referral strategies assessed by the original NICE model.

Health economic uncertainty will be explored by changing the values of the equation variables to assess the robustness of the results. Due to the nature of the analysis with pre-

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determined equations, probabilistic sensitivity analysis will not be undertaken, therefore Cost Effectiveness Acceptability Curves (CEACs) will not be presented.

Model development
The health economic model results will be used as part of the iterative process to design the 'superior' BACKPACS referral strategy. The initial estimates for Baraliakos and BACKPACS referral strategies will be entered into the equations and cost-effectiveness estimated. The effectiveness (specificity/sensitivity/likelihood ratio), cost-effectiveness estimates and feasibility (ease of implementation) will all be part of the package of information on the strategies provided to the CoP and PPI groups for discussion. Factors included in feasibility considerations would include variables that might be completed at a single GPC consultation (i.e., presence of buttock pain, previous history of enthesitis or uveitis), versus factors that would require further evaluation or clinic attendance (i.e., response to NSAIDs or blood test results (CRP / HLA-B27). Any changes to the BACKPACS strategy will then be factored into the analysis and results re-estimated. A number of cycles of statistical and health economic modelling and then CoP/PPI consideration may be required, before an eventual 'superior' referral strategy is determined.

7. ADVERSE EVENTS

Reporting Requirements
The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

The risks of participating in this study are comparable to that of usual care. The clinical assessments are conceptually similar to what might have been done as part of usual practice. For example, participants may already be sent questionnaires about their condition and history before further clinical investigations take place. The clinical investigations in the study are all completed as per the NICE 2017 clinical guidelines for spondyloarthritis.

8. ETHICAL AND REGULATORY ASPECTS

8.1 Ethics Committee and Regulatory Approvals
The study will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, the UK Department of Health Policy Framework for Health and Social Care, 2017 and the Data Protection Act 2018.

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8.2 Informed Consent and Participant Information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both fully complete the electronic Informed Consent Form (eICF) before the person can participate in the study.

The eICF will be retained within the study database. Printable copies will be generated and retained within the Investigator Site File (ISF) and a copy will be made available electronically to the participant.

A copy will be filed in the participant's medical notes and note made in the notes that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasise to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to electronically sign a revised eICF.

If the eICF is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended eICF by the REC and use of the amended form (including for ongoing participants).

8.3 Records

8.3.1 Data Management

Arrangements for data handling will be specified in the Data Management Plan (DMP). This will include the agreed validation specification which will validate data for consistency and integrity as it is entered. Additional manual and electronic reviews may also be conducted, and data queries/clarifications may arise from such reviews.

Data will be held on clinical study servers. These servers are located within The University of Nottingham data centres, which are managed and monitored 24/7. Security is both physical (secure limited access) and electronic (behind firewalls, access via user accounts (username and password), restricted access – e.g. site user only has access to their sites data, and by user type/role). All access and data transactions will be logged in a full audit trail. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

The MRI scans will be stored at University College London (ICL), at the point of electronic transfer to UCL from the secondary care sites they will be pseudonymised with unique study identification number. The outcome of the review will be entered into RedCap.

Local secondary care centres will hold participant's contact information to ensure participants remain informed, this will be held in password protected databases on NHS computers in rooms with secure, limited access.

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Recordings of meetings will only be accessible to study members and may be made available to other members of the study team (e.g., PPI members). HRA procedures related to the Data Protection Act/ General Data Protection Regulation (GDPR) will be followed. Audio recordings will be deleted at the end of the study.

8.3.2 Case Report Forms

Data reported on each Case Report Form will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete CRFs will be trained to adhere to the study specific CRF completion guidelines.

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

Participant self-reported data collection (e.g., questionnaires) are completed electronically, and responses will be entered directly by participants onto the online data collection system.

Data queries will not be raised on participant completed questionnaires.

Participant questionnaires may also be completed with the research team by telephone, in which case the research team will access the eCRF to input responses, as reported by participants.

Each participant will be assigned a study identity code number, for use on workbooks, other study documents and eCRFs within the electronic database. The documents and database may also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

eCRFs will be treated as confidential documents and held securely in accordance with regulations.

Local data (at the secondary care site) to enable direct contact with patients (e.g., name, date of birth, address, email address, hospital number) will be held on a local password protected database. Information that is not required for the coordination of the study will not be shared outside of the local secondary care site.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Study Delegation Log.'

Any paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the eCRF.

8.3.3 Labelling

Each participant will be assigned a study identity code number for use on, consent forms and other study documents and the electronic database. The documents and database may also

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use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

8.3.4 Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. To allow for the accurate reconstruction of the study and clinical management of the participant, source data will be accessible and maintained.

Each site will record the location of source data at their site using a source data location log prior to commencing recruitment and signed by the Principal Investigator. Source data refers to, but is not limited to, the participant's medical notes, data recorded directly into the eCRF, participant paper questionnaires and source data worksheets (when direct entry to the eCRF is not possible).

All data collected directly from participants will be considered as source data within the eCRF. Where questionnaire data is collected in a paper worksheet, these data will be entered directly into the eCRF and will be considered source data.

8.3.5 Direct access to source data / documents

The eCRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

8.3.6 Site Set-up and Initiation

GP sites will be identified by local NIHR RDNs and will be Participant Identification Centre (PIC) sites. The study team will work closely with Principal Investigators and RDNs to provide training to individual PIC sites.

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to NCTU – this should be signed within the last 2 years. All members of the site research team will also be required to sign a site delegation and training log. Prior to commencing recruitment, all sites will undergo a process of initiation and will have completed any necessary training. Key members of the site research team will be required to attend either a meeting or a video call covering aspects of the study design, protocol procedures, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documents, instructions, and other documentation

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required for the conduct and reconstruction of the study. NCTU must be informed immediately of any change in the site research team.

8.4 Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using only their unique study identification number, on the Case Report Form and correspondence between the Trials Office and the participating site. The documents and database will also use their initials and date of birth (dd-mmm-yyyy) and the eCRF will only collect the minimum required information for the purposes of the trial.

The Investigator must maintain documents not for submission to NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that participant confidentiality is protected.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party, other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. Registries, Sponsor). Representatives of the IDEAL study NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

9. QUALITY ASSURANCE & AUDIT

9.1 Insurance and Indemnity

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

9.2 Study Conduct

Study conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the study; Study Delegation Log; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits);

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9.3 Study Data Monitoring and Audit

On-site monitoring
Triggered monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The study team will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Additional on-site monitoring visits may be triggered, for example by poor CRF return and completion, poor data quality, excessive number of participant withdrawals or deviations. If a monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU study staff access to source documents as requested.

Central monitoring
The NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. NCTU will check data entered onto the study database on an ongoing basis for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies.

Electronic consent forms will be subject to central review as detailed in the monitoring plan.

Study data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

Audit and Inspection
The Principal Investigator will permit study-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. The study will be subject to internal audit (system and study level) on a risk basis.

The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

Notification of Serious Breaches
The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that study or the protocol relating to that study. Sites are therefore requested to notify the NCTU of any suspected study-related serious breach of GCP and/or the study protocol. Where NCTU is investigating whether a serious breach has occurred, sites are also requested to assist NCTU in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to Programme Management Group, Programme Steering Committee, and the REC. This includes reporting serious breaches of GCP and/or the study protocol to the REC.

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9.4 Record Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Investigator site file, Trial Master File and study documents held by NCTU on behalf of the sponsor shall be archived securely in the Microsoft cloud which has multiple and redundant systems and backup services. This archive shall include all study databases and associated meta-data encryption codes. Access to files once archived (e.g. for inspection purposes) will be managed by the NCTU archivist and will only be accepted on approval of the University of Nottingham Sponsor.

Documents will be archived following any regulatory requirements and any local procedures. No documents will be destroyed without prior approval from the Sponsor.

9.5 Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Programme Steering Committee as appropriate in making this decision.

9.6 Statement of Confidentiality

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

9.7 Data Sharing

Participants' contact details, including name, address, telephone/mobile number and email will be shared between participating sites, NCTU and third parties i.e. Esendex, our text messaging provider and their sub-processors (where required) for the purposes of issuing questionnaires, appointments and electronic reminders (text/email) for the study.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team, NCTU researchers and the IDEAL-BACKPACS research team will have access to these data.

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Anonymised participant data may be shared with researchers external to the study research team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the Nottingham Clinical Trials Unit Data Sharing Lead, unless otherwise covered by a separate data sharing agreement.

10. PUBLICATION AND DISSEMINATION POLICY

Results of this study will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Chief Investigator and Programme Management Group and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator and NCTU. Manuscripts must be submitted to either party in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the study was performed with the support of University of Nottingham.

During the course of the study, press releases may be issued from NCTU. Presentations or other material prepared by local investigators to publicise the study must be reviewed by the Chief Investigator and NCTU. No party will be entitled to submit any publicity material without prior approval from NCTU.

Study participants will be asked whether they would like to receive a summary of the research findings and invited to leave contact details by which they will be contacted with the research summary at the end of the project, following the publication of results.

11. USER AND PUBLIC INVOLVEMENT

Patients and public will be involved at all stages, with Patient and Public Advisory Group (PAG) and a Community of Practice (CoP) advisory group informing the project throughout. These groups include individuals with recently diagnosed axSpA and those with non-inflammatory back pain. The PAG group have already provided helpful input into the study design at the grant application stage, and have reviewed the patient facing documents

12. STUDY FINANCES

Funding source

This study is funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (PGfAR) funder reference: NIHR205015.

Participant stipends and payments

Participants will not be paid to participate in the study but will receive a small monetary voucher, or travel reimbursement, of £15 to thank them for their time.

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SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)__Professor Jon Packham_____

Signature: J Packham, J Packham, (Nov 5, 2026 11:34:49 GMT)

Date: 5/11/2026

Study Statistician: (name)___Ms Cydney Bruce_____

Signature: C Bruce

Date: 6/11/2026

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Appendices

Appendix 1: Specification of the variables used for the ASAS-Criteria for classification of Axial Spondylarthritis

Clinical Feature of axSpA	Definition
Inflammatory back pain (IBP)	IBP according to experts: 4 out of 5 of the following parameters present: 1. Age at onset < 40 years 2. Insidious onset 3. Improvement with exercise 4. No improvement with rest 5. Pain at night (with improvement upon getting up)
Good response to NSAIDs	24-48 hours after a full dose of a non-steroidal anti-inflammatory drug (NSAID) the back pain is not present any more or much better. (the clinical co-applicants on the PGfAR IDEAL grant have concluded that response after one week would be more appropriate)
Arthritis	Past or present active synovitis diagnosed by a physician.
Dactylitis	Past or present dactylitis diagnosed by a physician.
Enthesitis	Heel enthesitis: past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus. (a broader evaluation of enthesitis is also being evaluated for the IDEAL study cohort)
Psoriasis	Past or present psoriasis diagnosed by a clinician.
Inflammatory bowel disease (IBD)	Past or present Crohn's disease or ulcerative colitis diagnosed by a physician.
Uveitis anterior	Past or present uveitis anterior, confirmed by an ophthalmologist.
Family history	Presence in first-degree or second-degree relatives of any of the following: a. Ankylosing spondylitis b. Psoriasis c. Uveitis d. Reactive arthritis e. IBD
HLA-B27	Positive testing according to standard laboratory techniques.
Elevated CRP	C-reactive protein above upper normal limit in the presence of back pain, after exclusion of other causes for elevated CRP concentration.

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