ScOttish Psoriatic artHritis Observational Study and biobank (SOPHOS)

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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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Protocol Approval

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1. ABBREVIATIONS

AE	Adverse event
ACR	American College of Rheumatology
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine transaminase
AST (SGOT)	Aspartate transaminase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body Mass Index
BP	Blood pressure
BSA	Body Surface Area
BSR	British Society of Rheumatology
CASPAR	ClASsification criteria for Psoriatic ARthritis
CCP	Cyclic Citrullinated Peptide
CRF	Case report form
CRP	C-reactive protein
CTIMP	Clinical Trial of an Investigational Medicinal Product
CVD	Cardiovascular Disease
DAPSA	Disease Activity index for Psoriatic Arthritis
DAS28	28 joint Disease Activity Score
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying antirheumatic drug
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESI	Events of Special Interest
ESR	Erythrocyte Sedimentation Rate
EQ5D	EuroQol five dimensions, 5 level scale
EULAR	European League Against Rheumatism
FACS	Fluorescence Activated Cell Sorter
GP	General Practitioner
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HADS	Hospital Anxiety and Depression Scale
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL	High density lipoprotein
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
IBP	Inflammatory back pain
ICH GCP	International Conference on Harmonization of Good Clinical Practice
LDL	Low density lipoprotein
LEI	Leeds Enthesitis Index
LFT	Liver function tests
MDA	Minimal Disease Activity
NAFLD	Non-alcoholic fatty liver disease
NICE	National Institute for Health and Clinical Excellence

NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area Severity Index
PBMC	Peripheral blood mononuclear cells
PETS	Patient Experience with Treatment and Self-management
PhGA	Physician Global Assessment
PIS	Participant Information Sheet
PROMIS™	Patient-Reported Outcomes Measurement Information System™
PROs	Patient Reported Outcomes
PsA	Psoriatic Arthritis
PsAID	Psoriatic Arthritis Impact of Disease
PsARC	Psoriatic Arthritis Response Criteria
PSS	Perceived Stress Scale
PtGA	Patient Global Assessment
RA	Rheumatoid Arthritis
REC	Research Ethics Committee
RF	Rheumatoid Factor
SAE	Serious adverse event
SCAR	Scottish Collaborative Arthritis Research network
SERA	Scottish Early Rheumatoid Arthritis
SF-12/36	Short Form survey – 12/36 questions
SMC	Scottish Medicines Consortium
SOPHOS	ScOttish Psoriatic artHritis Observational Study
SpA	Spondyloarthritis
UA	Undifferentiated Arthritis
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

2. STUDY SYNOPSIS

Title of Study	**S**c**O**ttish **P**soriatic arthritis **O**bservational **S**tudy and biobank (SOPHOS)
Study Centre:	Multi-centre
Duration of Study:	2 years initially, indefinite follow-up
Objectives:	To generate a molecular signature that describes and predicts the evolving psoriatic arthritis (PsA) phenotype. To compare and contrast this molecular signature with those being developed in Rheumatoid Arthritis (using comparator patients from the Scottish Early Rheumatoid Arthritis (SERA) cohort)
Methodology:	Observational cohort and Clinical Laboratory Study
Sample Size:	300
Inclusion Criteria	Adult patients (≥18 years) attending rheumatology clinics with *either*: 1. a new clinical diagnosis of PsA diagnosed by a rheumatologist *or* 2. an existing diagnosis of PsA, diagnosed by a rheumatologist, who are within 4 years of diagnosis (to allow later comparison with the RA patients in the SERA cohort). Recruitment will be limited to a maximum of 150 patients with recent onset PsA, ensuring at least 150 with newly diagnosed PsA. Any pattern of PsA is acceptable, provided diagnosis made or confirmed by a rheumatologist, with no minimum swollen or tender joint count requirement. Note: patients do *not* have to meet CASPAR criteria for inclusion into the study – fulfilment CASPAR criteria will be captured as part of data collection.
Exclusion Criteria	• Age <18 years. • Patients with an alternative rheumatological diagnosis such as rheumatoid arthritis, connective tissue disease or crystal arthropathy. • Patients who are currently on or who have previously received biologics or targeted synthetic DMARDs (such as apremilast or JAK inhibitors) [conventional DMARDs are allowed] • Hepatitis B/C or HIV infection
Statistical Analysis	Statistical analysis will be performed by statisticians and bioinformaticians in the Universities of Glasgow and Edinburgh involved in the SERA study and associated analyses, in addition to statisticians at UCB and other collaborators, as approved and appropriate for the biomarker studies being performed.

STUDY FLOW CHART	**Baseline visit**	**6 monthly follow-Up visits until 2 years**
Informed consent	X	
History		
Demographics – age, gender, marital status	X	
Post code for social deprivation score, educational attainment	X	
Smoking and alcohol history	X	X
Onset joint symptoms – date/ duration	X	
PsA diagnosis date	X	
Past medical history	X	
- Psoriasis – current/history of (inc. date onset)	X	X
- other SpA – uveitis, IBD (inc. date onset)	X	X
- inflammatory back pain	X	X
Family history – Psoriasis, other SpA, other conditions	X	
CASPAR criteria (components thereof)	X	
Comorbidities of interest (inc. hypertension, CVD, NAFLD, diabetes)	X	X
Medications = previous & current		
- DMARDs	X	X
- Other meds of interest (inc. steroids, NSAIDs)	X	X
Serious Adverse Events (SAEs) and Events of Special Interest (ESIs)	-	X
General assessment		
BMI = weight (kg), height (cm), waist & hip circumference (cm)	X	X
Blood pressure (BP)	X	X
PsA-related assessments		
66 Swollen Joint Count	X	X
68 Tender Joint Count	X	X
Dactylitis score (0-20)	X	X
Leeds enthesitis index (LEI; 0-6)	X	X
Physician Global Assessment for skin (PhGA_*skin*)	X	X
Body Surface Area (BSA) for skin	X	X
Nail involvement – Y/N and pitting/ onycholysis	X	X
Assessor/physician Global Assessment for PSA (PhGA_*PsA*)	X	X
Patient reported outcomes (PROs) and questionnaires		
Patient Global Assessment for PsA VAS (PtGA_*PsA*)	X	X
Patient assessment of skin (Pt_skin VAS)	X	X
Pain VAS	X	X
BASDAI	X	X
Fatigue – global fatigue VAS; chronicity; PROMIS-Fatigue 8A	X	X
DLQI	X	X
HAQ-DI	X	X
EQ-5D-5L	X	X
HAD Scale	X	X
Multimorbidity – Perceived Stress Scale (PSS)	X	X

Patient Experience with Treatment and Self-management (PETS)	X	X
Work Productivity and Activity Impairment (WPAI)	X	X
Psoriatic Arthritis Impact of Disease 12-item (PsAID-12)	X	X
Composite scores based on other assessments		
DAS28	X	X
Minimal Disease Activity (MDA)	X	X
Disease Activity index for Psoriatic Arthritis (DAPSA)	X	X
Blood tests and results		
Full blood count	X	X
ESR	X	X
CRP	X	X
Urea and creatinine	X	X
Liver function tests (LFTs)	X	X
Lipids	X	X
Glucose (if done routinely within 1 month of visit)	X	X
RF/CCP (if done routinely previously)	X	
Biobanking samples: (0, 6 & 12 months only)[3] - Blood - Urine for proteomics/metabolomics	 X X	(6 & 12 mo only)[3] X X
Imaging		
X-ray Hands and Feet	X[1]	12 months only[2]
Record dates of previous imaging of interest	X	X

[1.] Baseline x-rays of hands and/or feet do not need to be repeated if these were already done within 6 months of baseline visit.

[2.] X-rays of hands and/or feet at 12 month visit do not need to be repeated if already done within 1 month of this visit.

[3] Where month 12 study blood and urine samples were not collected due to site activities being temporarily halted due to COVID restrictions OR where visit was undertaken using remote means, the study samples can be collected at the following scheduled visit

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that occurs in 7-39% of patients with psoriasis[1,2] and results in pain, stiffness, joint damage and consequent disability. Psoriasis itself is a common skin condition, affecting both genders across age spans, and occurs in 1.3-2.2% of the UK population [3]. Both psoriasis and PsA have a significant negative impact on quality of life, affecting psychological, functional and social domains [4]. Both are associated with reduced life expectancy [5] as a result of significant comorbidity, including increased cardiovascular disease, obesity, metabolic syndrome and diabetes [6,7].

While there have been significant advances in the management of PsA, these are based mainly on therapies adopted from rheumatoid arthritis (RA) and, more recently, psoriasis. There remains significant unmet need, with many patients only responding partially or in only one tissue compartment, and a substantial minority who fail to respond at all. Treatment decisions remain based mainly on empirical “trial and error” rather than objective measures.

PsA is clinically heterogeneous condition potentially involving synovium, enthesis, bone and skin; this broad spectrum of target tissue involvement represents arguably the major challenge in improving treatment and thus addressing unmet need. Historically, clinical classification is based on dominant anatomical location/distribution of disease and to some extent rate of progression [8]. Increasingly, these sub-types are recognised to have distinct genetic, imaging and immunologic profiles though such distinctions are not yet reflected in classification of disease or clinical practice. Nevertheless, treatment guidelines proposed by GRAPPA and EULAR recognise broad anatomically based classifications in their recommendations, particularly reflecting peripheral arthritis (synovitis rich), enthesitis / dactylitis and axial-predominant disease [9,10]. Many patients however do not conform to one discrete clinical sub group in practice and application of such algorithms is not facile.

Therapeutic responses in PsA, although improved in the last decade remain suboptimal. Treatment strategies for PsA have been adapted mainly from those used in RA, with generally disappointing results. While the advances in combination disease modifying anti-rheumatic drug (DMARD) therapy, treat to target strategies, and targeted biologics therapies have revolutionised the management of RA, the results in PsA have been more modest. TNF inhibitors are effective medicines in a proportion of PsA patients but their use in PsA followed their successful development in RA and was not driven by a persuasive role for TNF in PsA *a priori*, while other 'therapeutic transitions' have met with modest or no success when applied in PsA (e.g. abatacept, tocilizumab, rituximab) emphasising the need for a re-evaluation of the approach to new therapeutics in this disease. Increased understanding of the pathogenesis of psoriasis, and to a lesser extent PsA, particularly relating to the role for the IL-17/IL-23 axis, has led to the development of several new agents (e.g. ustekinumab, secukinumab). A phosphodiesterase-4 inhibitor (apremilast) I snow also available and other small molecule inhibitors (e.g. tofacitinib) are likely to reach the market over the next few years. However, despite the increase therapeutic options, treatment choice in clinical practice remains largely driven by physician and patient preference and cost, rather than any objective prognostic markers.

The occurrence of dichotomous responses whereby skin or articular structures respond with different magnitude or even direction to a given therapeutic is perplexing and points to distinct molecular processes in individual patients and even tissue compartments. The outcomes noted in recent therapeutic studies targeting the IL-17/23 axis are also intriguing in this regard in offering very robust responses in the skin, and enthesis, but perhaps less consistent benefits in the synovial compartment – these observations are consistent with the hypothesis that discrete inflammatory pathways may operate across different tissue compartments even for a given pathogenic challenge.

Other pertinent challenges deserve consideration. For many years the outcome measures used to guide new drug generation and strategy studies were 'borrowed' from the RA literature, or taken directly from dermatology practice and often did not faithfully reflect the clinical presentation, change in state or response capacity in the context of PsA. In this respect the development of PsA specific outcomes (e.g. DAPSA) and targets (e.g. MDA) is encouraging and will in due course provide clinical tools to enhance trial design and decision-making.

The rapid growth of biologic agents for the treatment of rheumatic conditions, particularly conditions such as PsA with multiple components, demands a better, more targeted use of these expensive and potentially toxic treatments. It is therefore crucial to be able to predict likely outcomes (in terms of disease phenotype, prognosis and response to therapy) early in the disease course in order to facilitate timely, appropriate, cost-effective intervention in a stratified, targeted manner. In particular, it is likely that to achieve step-change progress in PsA, appropriate stratification and thus optimisation of therapy will be dependent on the early recognition of their evolving clinical phenotype that in turn reflects the dominant underlying pathophysiology. ***Herein we will test the hypothesis that a molecular signature can be derived from a combination of genomic and transcriptomic sequence analysis that will predict the phenotypic evolution of patients who present with early inflammatory arthritis / enthesitis on a background of psoriasis***. Once identified, such a signature will facilitate more effective early intervention and stratification. This is of particular, contemporaneous importance given the expanding variety of novel modes of action in the therapeutic armamentarium. The study will also yield important information regarding the burden, natural history and pathogenesis of PsA. The study proposed will build on our existing Scottish Early Rheumatoid Arthritis (SERA) study and associated infrastructure, utilise the extraordinary strengths in e-Health environment in Scotland and feed into the developments in precision medicine, exemplified in the Stratified Medicine Scotland - Innovation Centre, and will thereby place the Scottish investigational network at the forefront in this important expanding field.

1. STUDY OBJECTIVES

5.1 Primary objectives:

- to generate a molecular signature that describes and predicts the evolving psoriatic arthritis (PsA) phenotype.
- To compare and contrast this molecular signature with those being developed in Rheumatoid Arthritis (using comparator patients from the SERA cohort)

5.2 Key research questions:

1. Can a molecular signature in new onset and early PsA identify the discrete clinical phenotypes that evolve in PsA?
2. Does the molecular signature allow us to further refine the phenotypes?
3. Can the molecular and genetic signature in early PsA predict outcomes of clinical relevance? (these include predictors of poor or good prognosis, response to therapy)
4. Can the molecular signature distinguish early PsA from matched patients with early RA and undifferentiated inflammatory arthritis (UA) in an existing study (SERA)?
5. How do treatment burden, clinical and psychological factors influence outcomes in PsA?

6. STUDY DESIGN

A national cohort of patients with new or recent onset (≤4 years of diagnosis) with prospective data collection, every 6 months for two years, and linked biobank collection.

6.1 Setting: Secondary care rheumatology units across Scotland

6.2 Outcome measures

The important outcomes collected will include:

- Clinical phenotype and associated molecular signature
- Disease activity (multiple domains, composite and low disease activity states)
- Comorbidities of interest (including cardiovascular and metabolic)
- Drug response, toxicity and requirement for biologics
- Radiographic progression (x-ray hands and feet)
- Patient reported outcomes (PROs)
- Hypothesis generation based on polyomic signatures

6.3 Sample size

We propose to collect 300 patients over a 24 month period (maximum 150 with recent existing PsA, ensuring a minimum 150 with newly diagnosed PsA). PsA is a less common than RA (UK prevalence of PsA ~0.5-0.7% and RA 0.8%) although the incidence of PsA in Scotland is unknown. Current estimate by SIGN of the prevalence of PsA in Scotland is 20000 people (http://www.sign.ac.uk/pdf/sign121.pdf). We will be recruiting both new and recent onset (≤4 years of diagnosis) patients, and as such we are confident that we will recruit at least 12-13 patients per month, thereby ensuring we achieve our recruitment target over 24 months. This would also ensure that by 36 months we will have at least 12 month follow-up on all patients.

7. STUDY POPULATION – INCLUSION AND EXCLUSION CRITERIA

7.1 Inclusion criteria

Adult patients (≥18 years) attending rheumatology clinics with *either*:

1. a new clinical diagnosis of PsA diagnosed by a rheumatologist *or*
2. an existing diagnosis of PsA, diagnosed by a rheumatologist, who are within 4 years of diagnosis (to allow later comparison with the RA patients in the SERA cohort).

Any pattern of PsA is acceptable, provided diagnosis made or confirmed by a rheumatologist, with no minimum swollen or tender joint count requirement.

Note: patients do *not* have to meet CASPAR criteria for inclusion into the study – fulfilment CASPAR criteria will be captured as part of data collection.

7.2 Exclusion criteria

Patients who meet ANY of the following will not be eligible for the study:

1. age < 18 years,
2. alternative inflammatory rheumatological diagnosis** (such as RA, gout, connective tissue disease). [**Note: Concomitant osteoarthritis is permitted]
3. patients who are currently on or who have received biologic or targeted synthetic DMARDs (such as apremilast or JAK inhibitors) [conventional DMARDs are allowed]
4. known to have Hepatitis B/C or HIV infection

7.3 Informed Consent

Patients who are found to be eligible for the study will be given verbal and written information about the study. Written, informed consent will be obtained from all patients who agree to participate in the study. Consent will be sought for the collection of personal data, data linkage, collection, storage and analysis of samples (now or in the future) in the biobank, and willingness to join a research register to be contacted about relevant future research studies.

7.4 Recruitment

Potential participants will be approached about the study by a member of their usual clinical team by one of two routes:

Firstly, most potential participants (and all newly diagnosed patients) will initially be approached about the study at the time of their visit to the rheumatology clinic. They will be informed by their routine care team that there is an ongoing PsA study, given the participant information sheet (PIS) to read and asked if they would be happy for the research nurse to contact them to see if they would be interested in participating. Some patients attending rheumatology units (particularly in rural areas) travel considerable distances to attend their routine clinic appointment, and others are in full time employment. Such patients may desire, in principle, to contribute to the research but be unable/unwilling to return to the hospital for a second visit >48 hours after they receive the PIS in clinic. Therefore, if after speaking to the research nurse and reading the PIS, patients express an interest in taking part in the study we propose to offer them two choices:

(1) The default position is that patients will be offered the possibility of coming back for another appointment to take part in the study at their convenience, but after an interval of 48 hours or more,

(2) Patients who express a preference to perform the study visit on the same day will be offered the possibility of consenting to take part in the study at the time of the appointment.

The following safeguards are proposed in order to avoid any suggestion of coercion: no patient will be put under pressure to consent on the day of attendance, and any patient who wishes to consider their involvement and to return for another appointment will be free to do so (this will be the default option); in the event that a patient expresses a desire to give consent on the same day, the patients' attention will be drawn to the statement in the PIS that they are free to withdraw consent at any stage, without prejudicing their care and a research nurse will phone the patient at least 48 hours after the visit, in order to confirm that the patient is still willing to continue in the study. This is the standard procedure which has been used in the other local rheumatology observational studies and cohorts, including SERA.

As PsA is less common than RA and recruitment is therefore likely to be more challenging, we will also use a second method to identify and recruit patients in centres which have specialist PsA clinics. In these sites, a member of the usual clinical care team will review the records of patients attending the specialist PsA clinics and send an invitation letter and PIS to any patients diagnosed within the past 4 years. These patients would then need to contact the research nurse (“opt in”), via post (SAE) or phone, to indicate their potential interest before any further contact was made relating to the study. Members of the research team would not have access to any personalisable information until patients consent to participate in the study. Patients would only be sent the invitation once, with no follow-up for those who choose not to respond.

8. DATA COLLECTION

Patients will be reviewed bi-annually to year 2 and samples collected at baseline, six and twelve months. Where month 12 study samples were not collected due to COVID-19 study site restrictions

or where visits managed via remote means, study blood and urine samples can be collected at the next scheduled study visit.

Study visits: Participants will be reviewed, and samples collected at *baseline** and at *six monthly*† visits (unless otherwise indicated):

a. Demographics* – CHI number, age, gender, post code for social deprivation, marital status, educational attainment
b. Smoking and alcohol history*†
c. PsA history* – symptom onset, diagnosis date
d. Psoriasis history* – current or past history, date/age onset
e. Past medical history*† – including other spondyloarthritis (SpA) conditions (uveitis, inflammatory bowel disease); inflammatory back pain; family history (PsA, psoriasis, SpA); comorbidities of interest (including hypertension, cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), diabetes)
f. CASPAR classification criteria* (components thereof) [11]
g. Medication history*† - DMARDs, other medication of interest
h. Events of Special interest and Serious Adverse events†
i. General clinical measurements*† – weight (kg), height (cm), BMI, waist and hip circumference (cm), blood pressure
j. Psoriasis related assessments*† - body surface area (BSA) for psoriasis; nail involvement (yes/no, pitting, onycholysis); assessor/physician global assessment of skin (PhGA_skin; as VAS)
k. PsA related assessments*† - 66/68 swollen and tender joint counts (distribution and score); dactylitis score (present/absent; 0-20); Leeds enthesitis Index (0-6); assessor/physician global assessment of PsA (PhGA_PsA; as VAS)
l. Patient-reported outcomes (PROs)*†:
    - 1. patient global assessment of PsA (PtGA_PsA); 2. patient pain VAS; 3. patient assessment of skin (Pt_skin VAS)
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);
    - DLQI; HAQ-DI; EQ-5D-5L;
    - Fatigue – global fatigue VAS, chronicity and PROMIS-Fatigue 8A
    - Hospital Anxiety and Depression survey (HADS)
    - Employment; Work Productivity and Activity Impairment (WPAI)
    - Multimorbidity: PSS and PETS
    - Impact of Disease: PsAID-12
h. Composite scores (based on above measures)*†:
    - DAS28
    - Minimal Disease Activity (MDA)
    - Disease Activity index for Psoriatic Arthritis (DAPSA)
    - Response criteria (where appropriate): Psoriatic Arthritis Response Criteria (PsARC)
i. Routine laboratory tests and results*†:
    - 1. Full blood count; ESR
    - 2. CRP; urea and creatinine; liver function tests (ALT, AST, ALP depending on local availability)
    - 3. Lipids: total cholesterol, LDL, HDL and triglycerides (depending on local availability)*

Results of routine laboratory tests done within 1 month of visit can be used.

- Glucose result: where available (within 1 month of assessment)
- RF/CCP result: where available (no time-limit)

j. Biological samples for determining the molecular signature and biobanking*† (baseline, 6 and 12 months only, except where month 12 samples not collected due to COVID -19 restrictions, samples can be deferred to the next scheduled visit):
   - a total of 55ml of additional blood will be collected from each patient comprising whole blood (RNA), PBMC (DNA), serum and plasma (for future immunoassays, metabolomics, RF and CRP) will be taken and stored at baseline, 6 and 12 months.
   - In addition, 5-10ml urine will be collected (proteomics, metabolomics)
   - where synovial fluid is being aspirated as part of standard clinical practice, synovial fluid (immunoassays) will also be collected and stored.

k. Imaging and radiographic reports*†:
   - plain digital radiographs of hands and feet for scoring of radiographic progression – performed at baseline[1] and 12 months[2]

     Note:

     [1.] Baseline x-rays of hands and/or feet do not need to be repeated if these were already done within 6 months of baseline visit.

     [2.] X-rays of hands and/or feet at 12 month visit do not need to be repeated if already done within 1 month of this visit
   - dates of any previous imaging of interest (see list below), performed as part of standard clinical practice, will be captured. Imaging results will not be captured at this point, but will allow images or results to be accessed later, if required:
     i. previous x-rays hands or feet
     ii. x-ray pelvis/sacro-iliac joints
     iii. x-ray spine
     iv. musculoskeletal ultrasound
     v. musculoskeletal MRI
     vi. ultrasound liver
     vii. fibroscan

Data will be entered on customised eCRF developed by the study team using the Castor EDC. PROs will initially be captured using paper versions which will then be transcribed onto the eCRF. The project manager and study team will co-ordinate data validation checks and query resolution via this system.

Training

To aid standardisation of examination techniques, research nurses involved in collecting metrology data and biological samples will attend a one day training day before the study starts, while refresher training courses will be run periodically during the study as required.

9. SAMPLES AND BIOBANK

9.1 Routine clinical laboratory tests

Routine blood tests (FBC, ESR, urea/creatinine, LFTs, CRP) performed to assess clinical activity, disease comorbidity and monitoring of treatments will be performed by NHS laboratories.

Where performed routinely, results of lipids and glucose samples taken within 1 month of visit will be recorded. Where available, results of previous RF and/or /CCP (no time limit) will be recorded in the eCRF. [Total volume routine clinical bloods ~10ml/visit].

9.2 Research and biobank samples

We will employ an established protocol and standard operating procedures to collect samples to derive a molecular signature. Sites will be provided with collection kits for study samples. Urine and up to 35-55ml (depending on whether site able to process whole blood for flow cytometry as per table below) of additional blood for research samples will be collected from patients comprising whole blood, PBMC, serum and plasma will be taken and stored (or analysed) at baseline, 6 and 12 months[#] (as shown in table below). If recommended by the project Steering Committee and funds allow, up to 55 mls of blood and 10ml urine may be taken at later/ annual visits thereafter (the sample types and collection tubes being determined by the Scientific Steering Committee as required, according to the needs of the project). Additional approval from the REC would be sought prior to this.

Biological Sample Collection and storage

Sample type	Collection Tube	Volume	Lab Analysis	Aliquots	Sample storage
NHS Samples: Processed by local NHS labs					
Routine haematology	EDTA	5ml	FBC, ESR	N/A	N/A
Routine biochemistry	SST	5ml	U&Es, LFTs, CRP Lipids	N/A	N/A
Research samples:					
Whole Blood	Paxgene RNA	2.5ml x 2	RNA	None	-80°C
Whole Blood	EDTA	5ml	DNA	5 x 1ml	-80°C
Whole Blood**	EDTA	10ml x 2	Flow cytometry	4 x 1ml (as PBMCs)	-80°C (short-term), then liquid nitrogen (long-term)
Serum	SST/Plain	10ml → 4ml	Immunoassay; RF and CRP	10 x 400ul	-80°C
Plasma	Lithium	5ml → 2ml	Immunoassay	5 x 400ul	-80°C
Plasma	EDTA	10ml → 4ml	Metabolomics	10 x 400ul	-80°C
Urine	Universal container	5-10 ml	Proteomics, metabolomics	4 x 1ml	-80°C

[#] Except where month 12 blood and urine samples not collected due to COVID-19 restrictions, samples can be collected at the next scheduled visit.
** Whole blood for flow cytometry will only be performed at selected sites with appropriate laboratory facilities to perform required PBMC protocol.

Samples may be stored temporarily in local biorepositories in the academic teaching centres or NHS Clinical Research Facilities before being centralised as part of the accredited NHS Greater Glasgow & Clyde Biorepository. Samples will be made available to all academic researchers for ethically approved studies, subject to the approval of the SOPHOS Access Committee. The remit of the SOPHOS Access Committee is outlined in Section 12.3.

Periodically, some patients will attend for scheduled or unscheduled visits at which they require therapeutic or diagnostic aspiration of synovial fluid. After using any fluid required for diagnostic purposes, the residual synovial fluid will be used for analysis and storage in the biobank.

10. SAFETY REPORTING

As this is an observational study, the NHS Health Research Authority (HRA) rules for safety reporting in research other than CT-IMPs will apply, as outlined on the HRA website http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-%20safety-reporting/

For safety reporting for research other than CT-IMPs, the HRA defines a Serious Adverse Event (SAE) as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant should be reported to the REC where in the opinion of the Chief Investigator the event was:

- "Related" – that is, it resulted from administration of any of the research procedures, **and**
- "Unexpected" – that is, the type of event is not listed in the protocol, PIS or SmPC, as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs (Appendix 1). There is no requirement to provide reports to RECs other than the main REC.

The Chief Investigator should include a report on the safety of participants in the annual progress report to the REC.

In addition, we have compiled a list of Events of Special Interest ESI: a list of clinical events that we believe, while not necessarily constituting an SAE, are or particular clinical interest and warrant additional data collection – for example pregnancy, or flares of psoriasis. These are shown in Appendix 3. However, this list may be expanded, as needed – for example, if new information comes to light suggesting a specific safety signal for one of the pharmaceutical agents included in the study.

11. STATISTICAL ANALYSIS

Statistical analysis will be performed by statisticians and bioinformaticians in the Universities of Glasgow and Edinburgh, including those already involved in the SERA and associated analyses, in addition to statisticians at UCB and other collaborators, as determined and appropriate for the biomarker studies being performed.

Initial analysis will involve description of baseline characteristics and comparison between different clinical phenotypes. Thereafter, because the study is designed to able to answer a number of different research questions, the precise analysis will depend on the specific question being asked.

12. RESEARCH GOVERNANCE

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). Ethical approval will be sought from an NHS Research Ethics Committee (REC), and local NHS R&D from each participating site, prior to the start of the study.

12.1 Peer review

The study was initially reviewed internally within the research group and subsequently externally peer-reviewed by the Chief Scientist's Office, as part of a competitive funding application process, and also by UCB Pharma's internal scientific committee.

12.2 Confidentiality

Data will only be obtained from consented study participants. The initial approach to potential participants will be made by a member of the patient's usual care team. All data and samples will be anonymised using a unique subject identifier. Each participating clinical site will only have access to their local patients' information only. Investigators and SOPHOS research staff based at the University of Glasgow will have access to all study information in order to maintain the database and conduct data management, and coordinate patient follow-up. Identifiable data will only be accessed or recorded for patients who have given consent to participate in the study as this is a condition of entry into the study.

12.3 Data protection

The Chief Investigator and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the Act. Access to complete participant data will be restricted to the Chief Investigator and appropriate study staff.

Participant names and contact details will be held separately from participant-reported data (questionnaires) and clinical data (gathered from medical records or input electronically by the local study team). Data will be stored on secure servers at the University of Glasgow. All data will be password-protected and only named study personnel will have access. Paper questionnaires returned to the University of Glasgow will be stored in locked filing cabinets.

Data and samples will be made available to all academic researchers for ethically approved studies, subject to the approval of the SOPHOS Access Committee, which involves patient representation.

The remit of the SOPHOS Access Committee will be to:

- establish a remit and code of governance;
- develop a pricing policy for access to samples in future studies;
- review applications from investigators for access to samples/clinical data;
- determine the scientific validity of the requests;
- evaluate demand on a finite biological sample collection;
- respond to requestors; and
- maintain alignment with ethical requirements.

Where permission to receive the data is granted, all data provided will be anonymised and provided with a subject identifier which will be unique to each dataset. Conditions of storage of the data, and length of time during which access is allowed will be detailed. The study team at the University of Glasgow will also maintain a register of who currently holds data from the study and length of access.

Published results will not contain any personal data that could allow identification of individual participants.

12.4 Protocol amendments

The Chief Investigator will seek approval for any amendments to the Protocol or other study documents from the Sponsor and NHS R&D offices; in addition, major amendments will also be sent for REC approval. Amendments to the protocol or other study documents will not be implemented without these approvals.

12.5 Protocol deviations and breaches

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

In the event that a serious breach of GCP is suspected, this will be reported to the Chief Investigator and the Sponsor immediately.

13. INDEMNITY AND INSURANCE

NHS Greater Glasgow and Clyde is the legal sponsor of the study and NHS-employed researchers will be covered for negligent harm through the NHS Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

14. FUNDING

The study is being funded by an educational grant from the Chief Scientist's Office and by an industry partner, UCB Pharma.

15. PUBLICATION AND ARCHIVING

It is anticipated that the results will be published in a peer reviewed journal. Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study on request. In accordance with the Research Governance Framework for Scotland 2nd edition 2006, data will be stored and archived by the University of Glasgow for a minimum of five years after conclusion of the study.

16. END OF STUDY

The end of the study is defined as database lock. The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study. A summary report of the study will also be provided to any parties providing funding for the study; any specific requirements for such reports can discussed.

17. KEY REFERENCES

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6. Raychaudhuri, S. K. *et al.* Increased prevalence of the metabolic syndrome in patients with psoriatic arthritis. *Metab Syndr Relat Disord* **8,** 331–4 (2010).
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APPENDIX 1: REPORT FORM FOR SERIOUS ADVERSE EVENT (SAE) – non-CTIMP
(For all studies except clinical trials of investigational medicinal products)

The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the Chief Investigator becoming aware of the event.

1. Details of Chief Investigator

Name:	
Address:	
Telephone:	
Email:	
Fax:	

2. Details of study

Full title of study:	
Name of main REC:	
Main REC reference number:	
Research sponsor:	
Sponsor's reference for this report: (if applicable)	

3. Type of event

Please categorise this event, ticking all appropriate options:

Death ☐	Life threatening ☐	Hospitalisation or prolongation of existing hospitalization ☐
Persistent or significant disability or incapacity ☐	Congenital anomaly or birth defect ☐	Other ☐

4. Circumstances of event

Date of SAE:	
Location:	

Describe the circumstances of the event: *(Attach copy of detailed report if necessary)*	
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	

5. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	

6. Acknowledgement of receipt by main REC (please insert name):
The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back to Chief Investigator (or other person submitting report)

Copy to be kept for information by main REC.

APPENDIX 2: Events of Special Interest (ESIs)

An event of special interest is a new event for which additional data is collected via the CRF, mainly relating to date of onset, relevant investigation results and treatment.
Information on ESIs would be included in the annual reports, along with cumulative SAEs. However, they would not be included in the expedited reporting of SAEs unless they fulfilled the criteria for this as listed in Section 10 (Safety reporting).

ESIs to be collected at each visit:

Cerebrovascular accident
Depression (new-onset) or suicidal ideation
Diabetes mellitus (new-onset)
Inflammatory bowel disease (new-onset)
Joint replacement surgery
Liver disease (new-onset; including NAFLD, but not isolated abnormal blood tests)
Malignancy (including pre-malignant conditions)
Myocardial infarction/ acute coronary syndrome
Pregnancy
Serious infection
Systemic candida or fungal infection
Uveitis (flare-up or new onset)