Scottish Early Rheumatoid Arthritis (SERA) inception cohort and biobank

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Sponsor	NHS Greater Glasgow and Clyde
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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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Funder

Chief Scientist's Office
Pfizer Inc

Protocol Approval

Study Title: Scottish Early Rheumatoid Arthritis (SERA) inception cohort and biobank

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TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
ACR	American College of Rheumatology
BSR	British Society of Rheumatology
CCP	Cyclic Citrullinated Peptide
CRP	C-reactive protein
CRF	Case report form
DAS28	28 joint Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
EC	Ethics Committee
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FACS	Fluorescent Activated Cell Sorter
GP	General Practitioner
HAD	Hospital Anxiety & Depression score
HAQ	Health Assessment Questionnaire
ICH GCP	International Conference on Harmonization of Good Clinical Practice
LDAS	Low disease activity state
NICE	National Institute for Clinical Excellence
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious adverse event
SERA	Scottish Early Rheumatoid Arthritis
SMC	Scottish Medicines Consortium
UA	Undifferentiated Arthritis
VAS	Visual Analogue Scale

STUDY SYNOPSIS

Title of Study:	Scottish Early Rheumatoid Arthritis (SERA) inception cohort and biobank
Study Centre:	Multi-centre
Duration of Study:	Indefinite
Objectives:	➢ to establish a comprehensive clinical database and biorepository from a large well characterized cohort of patients with newly-diagnosed undifferentiated arthritis (UA) and RA ➢ to capture prospective longitudinal data on patient-centred outcomes including remission, physical function, health-related quality of life and drug response/toxicity ➢ to facilitate translational research projects in UA and RA
Methodology:	National inception cohort
Sample Size:	1800 patients, 250 first degree relatives/friends, 120 TNFi treated patients
Inclusion Criteria	Patients with a new clinical diagnosis of rheumatoid arthritis or undifferentiated arthritis
Exclusion Criteria	Patients already on Disease Modifying Anti-Rheumatic Drug (DMARD) therapy for >6months and patients with an alternative rheumatological diagnosis (such as psoriatic arthritis, reactive arthritis, sero-negative spondyloarthropathy, connective tissue disease or crystal arthropathy) to explain their arthritis
Statistical Analysis	Statistical analysis will be performed by the Robertson Institute of Biostatistics, University of Glasgow and Pfizer Research, Cambridge, MA, USA as determined by the biobank studies performed.

STUDY FLOW CHART

Visit	Baseline	1	2	3	4	5+
Month	0	6	12	18	24	Annual
Informed consent~	x					
RF/CCP*	x					
Swollen joint count	x	x	x	x	x	x
Tender joint count	x	x	x	x	x	x
Patient global VAS	x	x	x	x	x	x
Assessor's global VAS	x	x	x	x	x	x
VAS Pain score	x	x	x	x	x	x
HAQ score~	x	x	x	x	x	x
HAD~	x	x	x	x	x	x
EQ5-D~	x	x	x	x	x	x
Fatigue Questionnaire	x	x	x	x	x	x
Work Questionnaire						x
Employment	x	x	x	x	x	x
Full blood count*	x	x	x	x	x	x
ESR/viscosity*	x	x	x	x	x	x
Urea/creatinine*	x	x	x	x	x	x
CRP	x	x	x	x	x	x
Lipids	x		x		x	x
Musculoskeletal US*	x	x	x			x
Adverse events		x	x	x	x	x
Medication	x	x	x	x	x	x
Biobank samples~	x	x	x		x**	x**

* depending on local availability
** restricted sample set (see p10)
~ also performed on first degree relatives

INTRODUCTION

Rheumatoid arthritis (RA) is the commonest inflammatory polyarthropathy. As such, it represents a disease state with global impact upon health status, associated with considerable socio-economic consequence [1]. In Scotland, RA affects approximately 35,000 patients [2]. It causes pain, stiffness, disability, reduced quality of life and premature mortality, the latter attributed primarily to cardiovascular co-morbidity. When patients first present to rheumatology services it can be difficult to make a definite diagnosis - many patients present with an undifferentiated inflammatory arthritis (UA) which over time may remit, remain undifferentiated, or differentiate into RA or other rheumatic disease (such as Psoriatic Arthritis). In most cohorts, only ~70% of patients who ultimately fulfil the ACR classification criteria do so at presentation, and the proportion is lower the earlier that patients are seen in their disease course. This is of some importance for this project because the emphasis in modern management of early RA is on prompt referral, early diagnosis and intensive management. It would be a great mistake, therefore, to recruit only patients with disease that already meets the ACR criteria for the diagnosis of RA – in many cases, critical therapeutic decisions need to be taken earlier on when diagnosis and prognosis remain uncertain. Indeed, predicting those patients with UA who will go on to develop RA, those who remit spontaneously, or those who will ultimately develop rapidly progressive disease is a major challenge.

Recently, advances in treatment have shown that improved outcomes in RA can be achieved by the use of intensive management strategies [3], combination disease-modifying anti-rheumatic drug (DMARD) therapy [4], and biologic therapy [5]. However, the prognosis of RA is highly variable: some patients respond to DMARD monotherapy, some require intensive combination therapy to achieve disease control, some require biologic therapy, and others have highly resistant disease that responds poorly to all available therapy. Whilst a number of prognostic factors (e.g. the presence of anti-CCP antibodies, erosion at presentation) have been shown to be predictive of functional and/or radiographic progression on a cohort level, none are sufficiently accurate to be able to direct therapy on an individual patient basis. This project will provide an invaluable resource for translational research by combining a carefully constructed prospective inception cohort with the prospective collection of important outcome measures, and an extensive biorepository.

The goal of individualised treatment strategies that maximise the likelihood of response whilst minimising the risk of toxicity, will require a complex integration of clinical, genetic and immunological variables. Our knowledge of RA pathogenesis (particularly synovial immuno-biology) has increased dramatically over a decade. Techniques amenable to the discovery of novel therapeutic targets and biomarkers have similarly evolved, and include genomics, proteomics, and FACS analysis. Their use will facilitate identification of targets, pathways and biomarkers associated with disease severity, progression and response/resistance to treatment. While previous efforts sought to utilise some of these techniques in isolation, we believe that only a careful integration of these approaches with high quality clinical characterisation and prospective follow up (i.e., “global profiling”), will deliver clinically meaningful results. SERA will provide the necessary resources for projects that seek to correlate cellular and molecular immunology with key outcome measures. The interpretation of the profiles will be greatly facilitated by the opportunity to match the results with first degree relatives who share a similar genetic profile.

STUDY OBJECTIVES

Primary objectives:

- to establish a comprehensive clinical database and biorepository from a large well characterized cohort of patients with newly-diagnosed undifferentiated polyarthritis (UA) and RA
- to capture prospective longitudinal data on patient-centred outcomes including remission, physical function, health-related quality of life and drug response/toxicity
- to facilitate translational research projects in UA and RA

STUDY DESIGN

A national inception cohort with prospective data collection every 6 months for two years and annually thereafter

Outcome measures

The important outcomes collected will include:

- clinical remission (DAS28<2.6)
- radiographic progression (change in Total Sharp Score [TSS] > 0.5)
- rapidly progressive disease (change in TSS in top quintile)
- drug toxicity
- serious co-morbidity

Sample size

The Clinical Audit of care of RA (CARA) was conducted in eight rheumatology units in Scotland employing 22 consultant rheumatologists, representing approximately 40% of Scottish rheumatologists. 489 patients were enrolled in two six-month periods which suggests that Scotland wide, approximately 1200 patients will be diagnosed with RA each year. This is compatible with the Public Health Institute of Scotland Needs Assessment Report which estimated that there would be 1699 incident cases of RA in Scotland. Not all rheumatologists or patients will agree to participate in the study but if 50% consent to participate, the inception cohort would recruit ~1800 patients over three years. If 250 first degree relatives/friends and 120 patients with established disease starting on TNF inhibitors are recruited the total study population will be ~2170 patients.

STUDY POPULATION

Inclusion criteria

Any patient with a new clinical diagnosis of undifferentiated polyarthritis (UA) or RA will be eligible. Patients must have $\geq$1 swollen joints.

Exclusion criteria

Patients 1) already on Disease Modifying Anti-Rheumatic Drug (DMARD) therapy for >6months 2) with an alternative rheumatological diagnosis (such as psoriatic arthritis, reactive arthritis, sero-negative spondyloarthropathy, connective tissue disease or crystal arthropathy) or 3) known to have Hepatitis B/C or HIV infection

Controls

1. First degree relatives – patients in the study or RA patients attending the rheumatology out-patient clinic may be asked to identify a first degree relative who would be prepared to donate blood to the biobank.
2. Friends - patients in the study or RA patients attending the rheumatology out-patient clinic may be asked to identify a friend of similar age, and same sex who would be prepared to donate blood to the biobank.
3. TNFi controls – patients with RA (according to the 2010 ACR/EULAR diagnostic criteria) who are embarking on their first course of biologic therapy with a TNF inhibitor (TNFi) as part of routine therapy will also be asked to consent to take part in the study, to act as an additional control group – this group comprises RA patients who have a disease phenotype that is resistant to conventional DMARD therapy, with a poor prognosis. Comparison of the SERA cohort with these patients will facilitate the identification of biomarkers of drug resistance or poor prognosis that can then be applied prospectively to the SERA cohort. Patients starting on TNFi will be seen at baseline and 6 months (or at discontinuation of the TNFi, whichever is sooner) for the same assessments as the SERA cohort and will donate

the same biobank samples. SERA patients who subsequently start TNFi therapy may be recruited to both cohorts.

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, collection, storage and analysis of samples (now or in the future) in the biobank, and willingness to join a research register.

Control subjects will receive an information sheet about the study via the patient. If they agree to participate, written consent will be obtained for the collection, storage and future analysis of their samples.

DATA COLLECTION

Patients will be reviewed and samples collected at baseline, six and twelve months. The clinical cohort will be followed up bi-annually to year 2 and then annually thereafter

a. Demographics – age, gender, ethnicity, Carstairs index, marital status, CHI number
b. Employment – Work Productivity and Activity Impairment Questionnaire (WPAI)
c. Referral – date of symptom onset, date of referral and date of diagnosis
d. Past medical history, smoking history, alcohol intake, drug therapy
e. ACR/EULAR 2010 classification criteria
f. Clinical – BMI, swollen joint count, tender joint count, patient global assessment of disease activity (VAS 0-100mm), assessor's global assessment of disease activity (VAS 0-100mm), pain score (VAS 0-100mm), duration of morning stiffness, disease activity score, Health assessment questionnaire, Hospital Anxiety and Depression questionnaire, EQ5-D questionnaire and fatigue questionnaire.
g. Laboratory and radiographic – urea, creatinine, full blood count, ESR or plasma viscosity, CRP, total cholesterol, HDL-cholesterol, rheumatoid factor and/or anti-CCP antibodies, appearances at musculoskeletal ultrasound (where performed) and plain digital radiographs of hands and feet. Radiographs are performed at baseline, 12 and 24 months and annually thereafter where taken as part of routine NHS care, Subjects enrolled in the SNAP cohort will undergo hand xrays at month 6 visit.

All control subjects will be asked to complete the four questionnaires (HAD, HAQ fatigue and EQ5-D). First degree relatives and Friends will not require clinical assessment and will be assessed once. TNFi treated controls will receive the same assessments as the SERA patients, and will be assessed twice, at baseline and after 6 months of TNFi therapy (or at the point of discontinuation if this occurs earlier than 6 months).

Data will be entered on an eCRF developed by the Robertson Centre, University of Glasgow who will also co-ordinate data validation checks and query resolution.

Training

Research nurses involved in collecting metrology data will attend a one-day training day, before the study starts, to aid standardisation of examination techniques.

BIOBANK

Biological samples for Biobank – urine and up to 100ml of blood will be collected from patients comprising whole blood, PBMC, serum and plasma will be taken and stored (or analysed) at baseline, six and twelve months. Up to 50mls of blood and 5ml urine may be taken at 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). Similar samples would be collected from control subjects at baseline only (first degree relatives/friends), or baseline & 6 months (TNFi cohort).

Biological Sample Collection and storage

Sample type	Collection Tube	Volume	Lab Analysis	Aliquots	Sample storage
Whole Blood	Paxgene RNA	2.5ml x 2	RNA	None	-80°C
Whole Blood	EDTA	5ml	DNA	5 x 1ml	-80°C
Serum	SST/Plain	10ml → 4ml	Immunoassay	8 x 500ul	-80°C
Plasma	Lithium	5ml → 2ml	Immunoassay	4 x 500ul	-80°C
Plasma	EDTA	10ml → 4ml	Metabolomics	8 x 500ul	-80°C
Whole blood	EDTA/Citrate/ Heparin	50mls	FACS, lymphocyte studies	None – used immediately	N/A
Urine	Universal container	4 mls	Proteomics, metabolomics	4 x 1ml	-80°C

Samples may be stored temporarily in the SAHSC biorepositories in the academic teaching centres before being centralised in the Greater Glasgow & Clyde NHS Biobank. Samples will be made available to all academic researchers for ethically approved studies, subject to the approval of the SERA Access Committee which involves patient representation. The remit of the 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.

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. Patients will be asked to donate 20mls whole blood collected in EDTA for immediate FACS analysis. Both blood and synovial fluid samples will be transferred directly to the labs in Aberdeen or Glasgow University before onward transfer to the AHSC nodes and biobank.

STATISTICAL ANALYSIS

Statistical analysis will be performed by the Robertson Centre for Biostatistics, University of Glasgow and by Pfizer Research Cambridge, MA, USA as determined by the biobank studies performed.

INDEMNITY AND INSURANCE

NHS employed researchers will be covered for negligent harm through the NHS Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

FUNDING

The study is being funded by an educational grant from the Chief Scientist's Office and by Pfizer Inc.

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. Data will be stored and archived by the Robertson Centre for Biostatistics, University of Glasgow for a minimum of five years.

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