# The Norfolk Arthritis Register (NOAR)

## Study Protocol

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Chief Investigator</th>
</tr>
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</table>
| Name: University of East Anglia  
Address: Faculty of Medicine & Health Sciences  
Norwich Research Park  
Norwich  
NR4 7TJ  
Contact: Tracy Moulton  
Telephone: 01603 591482  
Email: t.moulton@uea.ac.uk | Name: Professor Alex Macgregor  
Address: Bob Champion Research and Educational Building  
James Watson Road  
University of East Anglia  
Norwich Research Park  
Norwich  
NR4 7UQ  
Telephone: 01603 593570  
Email: a.macgregor@uea.ac.uk |
### Co-investigators

<table>
<thead>
<tr>
<th>Name: Suzanne Verstappen, Research Fellow</th>
<th>Name: Dr Tarnya Marshall, Consultant</th>
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<tbody>
<tr>
<td>Address: Arthritis Research UK Epidemiology Unit</td>
<td>Address: Norfolk and Norwich University Hospital</td>
</tr>
<tr>
<td>University of Manchester</td>
<td>Department of Rheumatology</td>
</tr>
<tr>
<td>Stopford Building</td>
<td>Colney Lane</td>
</tr>
<tr>
<td>Oxford Road</td>
<td>Norwich</td>
</tr>
<tr>
<td>Manchester</td>
<td>NR4 7UY</td>
</tr>
<tr>
<td>M13 9PT</td>
<td>Telephone: 01603 287677</td>
</tr>
<tr>
<td>Telephone: 0161 275 5663</td>
<td>Email: <a href="mailto:tarnya.marshall@nnuh.nhs.uk">tarnya.marshall@nnuh.nhs.uk</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:Suzanne.verstappen@manchester.ac.uk">Suzanne.verstappen@manchester.ac.uk</a></td>
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### Study Team

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<tr>
<th>Name: Jackie Chipping, Clinical Manager</th>
<th>Name: Jackie Chipping, Clinical Manager</th>
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<td>Address: Norwich Medical School</td>
<td>Address: Norwich Medical School</td>
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<td>University of East Anglia</td>
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<tr>
<td>NR4 7TJ</td>
<td>NR4 7TJ</td>
</tr>
<tr>
<td>Telephone: 01603 597204/5</td>
<td>Telephone: 01603 597204/5</td>
</tr>
<tr>
<td>Email: <a href="mailto:noar@uea.ac.uk">noar@uea.ac.uk</a></td>
<td>Email: <a href="mailto:noar@uea.ac.uk">noar@uea.ac.uk</a></td>
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BACKGROUND
The Norfolk Arthritis Register (NOAR) is a large community based, long-term observational study investigating the cause and outcome of inflammatory polyarthritis (inflammation and swelling of the joints). The Register is funded by the Arthritis Research UK Centre for Epidemiology (one of the UK’s leading medical charities). NOAR is based at the University of East Anglia and works in collaboration with the Department of Rheumatology at the Norfolk and Norwich University Hospital (NNUH) and the Arthritis Research UK Centre for Epidemiology at the University of Manchester. The purpose of the Register is to study the natural history of arthritis and to identify genetic and non-genetic factors which may be related to the onset of arthritis, response to treatment, and to long-term outcome. The study is registered on the UKCRN portfolio database and has recruited over 4000 participants since the study first commenced.

Starting in 1989, the Norfolk Arthritis Register recruits people who have developed an inflammatory arthritis whilst living in Norfolk, and who are willing to take part in research. All patients newly identified with inflammatory polyarthritis (IP), either presenting in primary or secondary care, are eligible to be referred to NOAR.

Previous publications from NOAR have established the incidence and prevalence of IP and Rheumatoid arthritis (RA) in the UK, have identified a number of novel risk factors for the developments of IP and RA, and have documented risk factors for the development of disability, joint damage demonstrated by x-ray progression, morbidity and mortality. NOAR has also published on the socio-economic effects of IP.

20 year cohort: NOAR continues to follow participants recruited to NOAR during 2000-2008 (Phase 1c) who are being followed for 20 years. The treatment philosophy for IP has undergone considerable change in the last 5-10 years therefore there is a need to continue to monitor this cohort.

Outcomes: to determine improved outcomes based on newer therapeutic options in comparison to treatments of 10-15 years ago.

CVD Study: Recruitment to this cohort commenced in January 2004 and completed in September 2008. The study has established certain risk factors for patients with IP. Part of the ongoing focus of the study is to continue to identify which participants with arthritis may be at increased risk of cardio-vascular disease and whether treatment of the arthritis reduces the risk. Participant involvement in this study in terms of additional examinations (such as carotid screening and ankle/brachial recording) concluded in 2013 when the remaining participants reached their 5th anniversary.

Outcomes: The NOAR study intends to follow the CVD cohort long-term to monitor any additional co-morbidity and mortality outcomes.

5 year cohort: NOAR continues to follow participants recruited to NOAR since 2013 (Phase 1e). This is a 5 year cohort for participants, recruitment for which is ongoing. We anticipate between 110-115 participant referrals per annum until the study closure of 31/07/2023 when accruals will be approximately 5330.

Outcomes: to study the natural history of IP in patients undergoing current treatment options, with particular regard to early arthritis.
MEMORY AND COGNITION IN RA (MACiRAS) – FEASIBILITY STUDY

The relationship between Rheumatoid Arthritis (RA) and memory function is poorly understood. Of the few studies that exist some show that RA may affect memory function others do not. It has been suggested that the anti-inflammatory medication used to treat RA may protect patients’ memory. We aim to examine the association between memory function and RA in a study of subjects enrolled in the Norfolk Arthritis Register. We will examine participants with a range of duration of disease and a range of exposure to anti-inflammatory and disease modifying medication.

In this feasibility study we will establish participant’s acceptance of a cognitive test battery. Participants will be drawn from the existing NOAR register who have met eligibility criteria and consented to take part in NOAR. It is anticipated 10no. assessments will be sufficient to test the validity of the assessments for this feasibility study. Participants will need to be aged 55 or over and consent to take part in this feasibility study by signing a further consent form.

Data on inflammatory arthritis has already been extensively collected for NOAR with more recent collation of a co-morbidity physician diagnosis of dementia information. However there is no standard method for collection of cognitive impairment within the NOAR framework. We intend to administer the following assessments:-

1. The Addenbrooke’s Cognitive Examination (ACE-III)\textsuperscript{11} is a cognitive test that assesses five cognitive domains: attention, memory, verbal fluency, language and visuospatial abilities.
2. INECO: frontal executive function\textsuperscript{12} is a test that measure frontal lobe brain function.
3. Social Cognition & Emotion Assessment – (mini-SEA)\textsuperscript{13} is a measure of the dorsol and ventro-medial frontal cortex.
4. Generalized Anxiety Disorder -7 (GAD-7)\textsuperscript{14}.
5. Patient Health Questionnaire -9 (PHI-9)\textsuperscript{15} this measure depression severity.
6. Rey Complex Figure test (RCFT)\textsuperscript{16} this measures recall.

These assessments will be scored according to their scoring protocol to assess whether the participant is showing memory decline or any other relevant findings. Any findings which raise concern about the participant’s wellbeing will be referred to the GP.

The assessments will be carried out by the NOAR Research Nurses who have received training in all the above cognitive assessments. Administration of the complete battery will take, on average, 1 hour.

We also intend to contact a family member or close friend whose name has been supplied to us by the participant. We will forward the Cambridge Behavioural Inventory (CBR-I-U)\textsuperscript{17} questionnaire by post including a pre-paid reply envelope. This questionnaire assesses various changes in the participant’s behaviour over the previous month which may have been noted by the relative/friend.
CURRENT NOAR STUDY AIMS AND OBJECTIVES

- To establish and follow a large and dynamic cohort of patients with IP.
- To collect medical and questionnaire data on relevant risk factors for development of IP.
- To collect samples of serum, plasma and DNA for serological & immunological study.
- To identify co-morbidity and mortality outcomes.
- To establish the risk of cardiovascular disease in comparison with the general population.

Eligibility/Inclusion criteria:

Currently, in order to be included in the register, individuals must be:

1. Aged 16 or over
2. Have had two or more swollen joints, lasting for 4 or more weeks
3. Resident in Norfolk at time of symptom onset and registered with participating GP Practice.
4. Onset in the last 2 years.
5. Willing to give informed consent to take part in the study.

Before 2009, NOAR recruited from primary and secondary care, providing patients were registered with a GP practice in the then Norfolk Health Authority. From 2009, NOAR limited recruitment to patients registered with practices participating in the European Prospective Investigation into Cancer (EPIC) study. This study is now closed to recruitment so it is planned to open up NOAR recruitment again to all GP practices within the South Norfolk, Norwich and North Norfolk Clinical Commissioning Groups.

PARTICIPANT IDENTIFICATION:

There are three sources of referrals to NOAR:

1. Opportunistic recruitment: GP practices:
   
   GPs/Practice Nurses/OTs/Physiotherapists notify NOAR of persons fulfilling the above criteria, provided verbal consent has been given, using a NOAR referral proforma.

2. GP practice Database Searches:
   
   GP practices to be invited to search their databases for eligible patients for NOAR. The GP practice send letters of invitation together with the patient information sheet to prospective participants inviting them to register interest direct to NOAR by means of a pre-paid response form.

3. Rheumatology Department staff, Norfolk & Norwich University Hospital:
   
   Medical staff/Rheumatology Practitioners/OTs/Physiotherapists notify NOAR of eligible patients using a NOAR referral proforma, provided verbal consent has been given.

A further method of participant identification is from Rheumatology Department clinic lists.
RECRUITMENT PROCEDURE

Please see Figure 1 below.

*Referrals received from GP/NNUH via a NOAR Referral proforma:*

NOAR team sends a letter of invitation and patient information sheet to the potential participant who are then contacted by telephone by a Research Nurse within 2 weeks to explain the study and provide an opportunity to ask questions. Inclusion criteria will be checked and willingness to participate confirmed. An appointment is made either at a hospital or GP surgery clinic or at the participant’s home. An appointment letter, consent form and patient questionnaire (CLINHAQ) is then posted or emailed to the participant and a unique 6 digit NOAR ID generated for each new participant.

*Referrals from GP database searches:*

On receipt of the response form from interested patients, a Research Nurse will make contact to explain the study, discuss eligibility and willingness to participate. Inclusion criteria will be checked and willingness to participate confirmed. An appointment is made either at a hospital or GP surgery clinic or at the participant’s home. An appointment letter, consent form and patient questionnaire (CLINHAQ) is then posted or emailed to the participant and a unique 6 digit NOAR ID generated for each new participant.

*Consent*

There are separate consent forms for both arms of the study reflecting the 5 year and 20 year cohorts. Participants will be asked to provide the following consent:

- Consent to collect and store questionnaire data
- Consent to collect and store biological data
- Consent for linkage of NOAR data to other national datasets (such as ONS for cancer & mortality, and for future record linkage via NHS Medical Research Information Service & Hospital Episode Statistics)
- Consent for samples of DNA to be passed, without identifying information, to other laboratories in the future for genetic studies in the cause and outcome of arthritis
- Consent to access patient hospital records/medical notes (this is undertaken only when it is of relevance to the research and undertaken by the named researcher).
- Participants may decline from the study at any point should they wish.
- Consent for linkage of NOAR data with information provided to the European Prospective Investigation into Cancer (EPIC) if the participant has taken part in that study as well.

*Consent for feasibility study: Memory and Cognition in RA*

There is a separate consent form for this feasibility study to establish participant’s acceptance of the memory and cognitive assessments. Participants already consenting to take part in NOAR will be asked to sign a further consent to take part in the feasibility study. Participants will be asked to provide the following:

- Consent to collect and store assessment data
- Consent to access patient medical records (this is undertaken only when it is of relevance to the research)
- Consent that their data will be recorded, stored and may be shared anonymously with other researchers.
- Consent to be contacted about research opportunities which may arise in the future.
• Consent to have their GP informed of their participation and any relevant findings, including information raising concerns regarding their wellbeing.
• Confirmation that they understand their participation in all parts of the feasibility study is voluntary, and they are free to withdraw without giving a reason and without this affecting their medical care or legal rights, and that this does not affect their main NOAR involvement.

Fig 1: NOAR Study Process Flowchart

BASELINE QUESTIONNAIRE

The baseline questionnaire will collect the following information:

Demographics
Date of birth, gender, ethnicity, occupation, employment status.

Family history
Identify any first degree relatives diagnosed with RA or psoriasis. Identify any first degree relatives diagnosed with an MI or a premature cardiovascular death.

Medical history
Co-morbidities (from a check list) and clinical history. Current prescribed medication. History of joint symptoms, joint surgery, fractures. Hospital attendance for arthritis.

Lifestyle questions
Smoking history and alcohol intake.
Reproductive history

Hormonal factors such as contraceptive use, pregnancy history (live births, miscarriage, still birth, termination), menopausal and hormone replacement history, hysterectomy

Examination

Examination of joints for tenderness, swelling and deformity. Height, weight, waist/hip circumference, blood pressure and pulse rate. (In the event of an abnormal blood pressure or pulse reading the result will be discussed with the participant and a letter will be given to the participant to follow up with their GP).

Serology

Latest ESR, CRP and Anti-CCP results are taken from patient hospital records.

Criteria applied at Baseline

Identified using the American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis 3: - Duration of morning stiffness, arthritis of 3 or more joint areas, arthritis to hand joints, symmetry, rheumatoid nodules.

Other questionnaires completed by participant

Health Assessment Questionnaire 1,2
EQ5D 6
BRAF-NRS 9
FALLS 10

BLOOD SAMPLES

All participants are asked to provide a blood sample at baseline which is used by the NOAR researchers to test for biochemical, hormonal, genetic and other factors which may influence the cause and outcome of arthritis. It is anticipated that at subsequent follow up assessments participants may be asked to provide a blood sample. Consent must be obtained prior to any sample being taken.

Samples are usually taken at the time of assessment by the NOAR Research Nurse, trained in venepuncture. On some occasions the participant may have the sample taken at their GP practice or at their local Rheumatology clinic. A 6ml EDTA and 5ml clotted blood sample will be taken. Samples are labelled with the participants NOAR unique ID number, assessment anniversary and date of collection. Serum is separated from the clotted sample and pipetted into aliquots and frozen. The EDTA samples are frozen whole. All samples are transported, still frozen, to the Norwich Biorepository, Norwich Research Park. In the case where samples will be collected by the participants GP, the blood sample collection kit will be provided to the GP. Samples will not be transferred outside the European Economic Area (EEA).

The serum of all participants will be tested for immunological markers including CRP and anti-CCP 8 which measure levels of inflammation in the blood. Rheumatoid factor will be also be measured to determine positive or negative results. Serum will be frozen and stored in aliquots for subsequent more detailed immunological analysis.

DNA will be extracted, measured, normalised and stored in matrix plates. Isolated DNA will be used for genetic analysis. The shared epitope (a group of genes know to be associated with RA), other candidate genes for susceptibility to or severity of IP, (in the past these have included MIF, TNF,
MBL). Any remaining DNA is stored and will be used in the future to test for other genes which are deemed relevant to the aetiology of IP or cardiovascular disease.

**FOLLOW UP ASSESSMENTS**

Participants are contacted each year at the anniversary of their original NOAR notification date (see Figure 2). Participants recruited to the study during Phase 1c are followed through to 20th anniversary with Phase 1e participants completing the study at 5th anniversary.

**Figure 2: PATTERN OF FOLLOW UP:**

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Arrangements are made for the participant to attend a NOAR clinic at the Norfolk & Norwich University Hospital, a participating GP surgery or a home visit. The Research Nurse completes a follow-up questionnaire which captures changes since last seen.

*Occupation/employment status*

*Medical and reproductive history*

Hormonal factors such as contraceptive use, pregnancy history (live births, miscarriage, still birth, termination), menopausal and hormone replacement history, hysterectomy

Co-morbidities (from a check list) and clinical history. Current prescribed medication, medication changes and reason why, recording start & stop dates. Joint symptoms, joint surgery & fractures since last seen. Hospital attendance for arthritis.

*Examination*

Examination of joints for tenderness, swelling and deformity may be undertaken by the Researchers. Height, weight, hip and waist circumference, blood pressure, pulse rate may also be measured. *(In the event of an abnormal blood pressure or pulse reading the result will be discussed with the participant and a letter will be given to the participant to follow up with their GP).* Latest ESR, CRP and Anti-CCP results are taken from patient hospital records. At 15th anniversary only the participant is asked to undergo spirometry, a non-invasive, painless examination using a hand-held spirometer which the participant blows into. This device measures lung capacity.

*Serology*

Latest ESR, CRP and Anti-CCP results are taken from patient hospital records.
Criteria applied at follow up

Application of ACR classification criteria for rheumatoid arthritis\(^3\) continues at subsequent anniversaries:-Duration of morning stiffness, arthritis of 3 or more joint areas, arthritis to hand joints, symmetry, rheumatoid nodules.

Lifestyle questions

Smoking history and alcohol intake.

Cardiovascular Questionnaire

An additional questionnaire relating to cardio-vascular events will be completed by the research nurse for those participants who were also part of the NOAR Cardiovascular study. Participant involvement in this study in terms of additional examinations (such as carotid screening) concluded in 2013 when the remaining participants reached their 5\(^{th}\) anniversary. However we still record any new CVD events in order to continue researching potential morbidity and mortality outcomes.

Other questionnaires completed by participant

Health Assessment Questionnaire\(^1\)\(^2\)
EQ5D\(^6\)
BRAF-NRS\(^9\)
FALLS\(^10\)
(All of these have been combined into one patient questionnaire called the CLINHAQ).

MRC Respiratory Symptoms Questionnaire\(^7\) at 15\(^{th}\) anniversary only.

BLOOD SAMPLES

All participants may be asked to provide a blood sample at each subsequent follow up assessment which can be used by the research to test for biochemical, hormonal, genetic and other factors which may influence the cause and outcome of arthritis.

Samples are usually taken at the time of assessment by the NOAR Research Nurse, trained in venepuncture. On some occasions the participant may have the sample taken at their GP practice or at their local Rheumatology clinic. A 6ml EDTA and 5ml clotted blood sample will be taken. Samples are labelled with the participants NOAR unique ID number, assessment anniversary and date of collection. Serum is separated from the clotted sample and pipetted into aliquots and frozen. The EDTA samples are frozen whole. All samples are transported, still frozen, to the Norwich Biorepository, Norwich Research Park. In the case where samples will be collected by the participants GP, the blood sample collection kit will be provided to the GP. Samples will not be transferred outside the European Economic Area (EEA).

The serum of all participants will be tested for immunological markers including CRP and anti-CCP\(^8\) which measure levels of inflammation in the blood. Rheumatoid factor will be also be measured to determine positive or negative results. Serum will be frozen and stored in aliquots for subsequent more detailed immunological analysis.

DNA will be extracted, measured, normalised and stored in matrix plates. Isolated DNA will be used for genetic analysis. The shared epitope (a group of genes know to be associated with RA), other candidate genes for susceptibility to or severity of IP, (in the past these have included MIF, TNF, MBL). Any remaining DNA is stored and will be used in the future to test for other genes which are deemed relevant to the aetiology of IP or cardiovascular disease.
CONSENT FOR LONG TERM FOLLOW UP (20 year study -Phase 1c)

Patients recruited in Phase 1c who have evidence of ongoing arthritis (who are currently or have been on disease modifying drugs or who have had evidence of active arthritis in at least one joint on at least two anniversary visits) are asked to continue with long-term follow-up, at 5th, 10th, 15th and 20th anniversaries. They are given a new information sheet and consent form to sign which addresses the long-term nature of the study.

POSTAL QUESTIONNAIRES

The 8th, 12th & 18th anniversary assessments are conducted by post. The questionnaire is completed by the participant and returned using a pre-paid envelope. The questionnaire is brief and covers joint symptoms, medication and includes a CLINHAQ.

DATA MANAGEMENT

University of East Anglia (UEA)
Each participant is assigned a unique 6 digit NOAR ID number. Personal identifiable information is entered manually and stored on a secure database at the University of East Anglia. The unique NOAR ID only is used for analysis. Investigators at UEA will carry out analysis of data on NOAR subjects. The database is password protected and is accessible to authorised personnel only.

Participants are interviewed and assessed using paper questionnaires. All paper documents are stored in locked filing cabinets in an office with restricted access. Anonymised data generated from the study will be held on a secure database and will be stored whilst there remain analyses worth undertaking. All anonymised questionnaires are subsequently scanned for reference and the images are stored by ID number on a dedicated network drive at the UEA, accessible only by authorised personnel.

Consent forms are also scanned and securely stored by ID number on the dedicated NOAR network drive but held separately from the questionnaires.

UEA shall act as Data Controller, joint with Manchester. A copy of the anonymised data is delivered to the University of Manchester via a secured drive with password protected access.

Data pertaining to study participants no longer being followed are archived in secure storage at the UEA.

Clotted and serum samples will be stored in monitored freezers and located in a secure biorepository within the Bob Champion Research and Education Building. Anonymised data generated from the study will be held on a secure database and will be stored whilst there remain analyses worth undertaking. Access to biological material and data generated from the study may be made available to other bona-fide researchers working in the field. Access to identifiable clinical data will not be permitted. Samples will not be transferred outside the EEA.

Arthritis Research UK Centre for Epidemiology, University of Manchester

Questionnaire data and data from biological sample analysis will be stored on a separate secure database linked by the anonymised ID within the Arthritis Research UK Epidemiology Unit at the University of Manchester. The database is password protected and is accessible to authorised personnel only.

Paper questionnaires and consents and stored in separate lockable filing cabinets in an office with restricted access within the Arthritis Research UK Epidemiology Unit.
The study teams at UEA and University of Manchester comply with all the aspects of the current Data Protection Legislation and the Universities’ own data security policies. The data managed shall be secured appropriately to protect against the consequences of breaches in confidentiality, failures of integrity or interruptions to the availability of that information. There are clear procedures for ensuring confidentiality by anonymising data and holding the data securely.

**ANALYSIS**

In NOAR different research questions are addressed and depending on the research question(s) appropriate statistical analysis will be applied including descriptive analysis, univariate and multivariate linear and logistic/ordinal regression analysis but also longitudinal data analysis such as random effect models and latent class growth models.

**DISSEMINATION**

*Peer-reviewed journals:* Since 1989, NOAR research has resulted in over 80 publications in peer-reviewed journals.

*NOAR Newsletter* - We send an annual newsletter to our research participants. The newsletter’s key objective is to maintain participant engagement in this longitudinal observational study. This newsletter provides lay summaries of study results as they emerge and provides an update on the study such as recruitment progress and highlight any administrative changes such as new members of staff and changes to contact details as well as other aspects of the study.

*Scientific Meetings* are held on an annual basis to which participants, their relatives, friends and carers, academics and clinical staff are invited to attend. The purpose of these meetings is to discuss NOAR future studies and dissemination any current findings.

*Patient Partners* – NOAR includes patient partners in all its strategic decisions, methodology & design of current and future studies.

**ETHICAL CONSIDERATIONS**

Recruitment to and participation in the study requires informed consent. A favourable ethics opinion will be sought for the identification and recruitment of potential participants, and for the collection of data and samples following informed consent.

A representative from the local arthritis patient group support is invited to attend the annual NOAR Management meeting. Participant representative(s) are also consulted and involved in assisting with the design and methodology of any new NOAR cohort studies. They are also consulted as to how information is explained, presented and disseminated, as required.

All efforts to reduce bias, data leaks and unnecessary release of patient information are ensured by strict adherence to ICH Good Clinical Practice, current Data Protection Legislation and Standard Operating Procedures governing the handling of data. All researchers and nurses are trained in good clinical practice (GCP).

**FUNDING**

This study is funded by Arthritis Research UK Centre of Excellence in Epidemiology grant. This stream of funding expires on 31st July 2018. A second term of funding for the Centre of Epidemiology has been approved commencing 1/8/2018 – 31/03/2023. We intend to change the method of data collection for NOAR in line with Arthritis Research UK recommendation to move towards digital machine readable data collection, analysis and linkage to multiple datasets.
TIMESCALE

We will continue to recruit participants for the duration of the current grant. Beyond this current grant investigators are in a position to apply for new grants to support cohort based projects and ongoing recruitment to the cohort.
REFERENCE LIST


