HTA TAR Final Protocol

HTA number 14/151/08

Final Protocol submitted 6th June 2016

1. Title of the project

The prognostic value of tests and assessment tools in rheumatoid arthritis

2. Name of TAR team and project lead

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3. Plain English Summary

Rheumatoid arthritis (RA) is a chronic condition that involves inflammation of the joints. There are around 400,000 people in the UK with RA.[1] RA can be extremely painful and cause serious problems in carrying out everyday tasks and reduced quality of life for patients. A range of treatment options are available to manage RA. The aims of treatment are to relieve the symptoms of RA and to minimise the build-up of joint damage.[1]

Clinicians would find it useful if they could identify at an early stage those RA patients who are most likely to suffer a worse course of disease (or prognosis). These patients could then be monitored closely so that they can receive appropriate treatment to minimise the health problems and joint damage due to RA.

It is not clear which of the available tests and assessment tools used in RA can best predict the course of disease in people newly diagnosed with RA and whether these also predict how well patients respond to drug treatment. The purpose of this work is to summarise the available evidence to support clinicians treating RA patients with the aim of identifying the patients who are most likely to have a worse course of disease as well as those most likely to respond to particular treatments.

4. Decision problem

4.1. Review question

What test or combination of clinical, laboratory, and imaging tests gives the best assessment of prognosis in RA and how well do they predict response to treatment?

4.2. Purpose of the decision to be made

The aims of this work are to:

i) systematically review the evidence relating to the use of selected tests and assessment tools in the evaluation of prognosis in patients with early RA, and

(ii) systematically review the evidence for the potential of selected tests and assessment tools as predictive markers of treatment response in patients with early RA

4.3. Definition of technology

The technologies of interest include blood tests, imaging modalities, and clinical assessment scores used in the evaluation of prognosis in patients with early RA. Specific tests and assessments to be included will be determined following scoping searches and consultation with clinical advisors.

4.4 Population

Patients with early RA

4.5 Setting

Any suitable setting (NB: it is anticipated that the majority of evidence will relate to secondary care)

4.6 Study design

Systematic review with appropriate pre-defined subgroup analyses

It is anticipated that the factors that are most likely to be of use for prognosis and prediction of treatment response will be assessed through meta-analysis of available aggregate level data. Development of a specific prediction model and the use of individual participant data (IPD) will not be considered.

4.7 Important outcomes

The prognostic and predictive performance of tests and assessment tools used either individually or in combination.

Prognostic performance will be considered in this assessment based on the association of the marker with clinical outcome. It can be thought of as a measure of the natural history of the disease. Predictive performance will be considered based on the association of the marker to response or lack of response to a particular treatment. A predictive factor implies a differential benefit from the treatment that depends on the level of the predictive factor. In statistical terms, this constitutes an interaction between treatment effect and the marker of interest.

In addition to measure of association for individual factors, measures of performance such as area under the curve (AUC), net reclassification improvement (NRI) and Royston discrimination measure (D) will also be considered, where reported. It is anticipated that these measures will be particularly relevant for evaluating specific combinations of factors.

Endpoints, against which prognostic and predictive markers are evaluated, will be specified following scoping searches and discussion with clinical advisors.

4.8 Other outcomes

Recommendations for future primary research

5. Report methods for synthesis of evidence of clinical effectiveness

Two linked systematic reviews will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/)[2] and informed by methods advocated by the Cochrane Prognosis Methods Group.

5.1 Search strategy

It is proposed that there will be two phases of searches: phase I scoping searches, followed by phase II full searches. The purpose of the phase I scoping searches is to determine the approximate extent of the evidence base relevant to the assessment. In the event that the phase I scoping searches identify a very large number of potentially relevant records, it may be necessary to adopt a pragmatic approach to ensure feasibility of the assessment, whereby additional limits may be applied to eligibility criteria (for example in terms of publication date, study design, size of study cohort, eligible tests and assessment tools etc). Following discussion of any such limits with clinical advisors, phase II full searches will subsequently be conducted.

Phase I scoping searches using keywords and specific study design filters will determine evidence available on prognostic and predictive factors in early RA. It is anticipated that the highly sensitive filter developed by the Hedges team at McMaster University will be used (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx). However, since the literature shows that explorative prediction research is difficult to find with any of the available filters,[3] searches will also be run relating to selected specific tests and assessment tools known to be used for prognostic purposes. This section of the search strategy will develop iteratively as further tests and markers are identified during the review.

In phase II, full searches will be carried out to identify evidence relating to selected factors identified through the scoping review. The comprehensive search strategy will comprise the following main elements:

Searching of electronic databases, registers and websites (as detailed below);
Contact with experts in the field;
Scrutiny of bibliographies of retrieved papers

Databases and registers:

MEDLINE and Medline in Process (Ovid); EMBASE; The Cochrane Library including the Cochrane Database of Systematic Reviews; CENTRAL (The Cochrane Central Register of Controlled Trials), DARE (Database of Abstracts of Reviews of Effects), NHS EED and HTA databases; Web of Science Conference Proceedings; Clinical Trials.gov; metaRegister of Controlled Trials.

Society and professional association websites:

The Cochrane Prognosis Methods Group; Arthritis Research UK; British Society for Rheumatology; National Rheumatoid Arthritis Society; OMERACT Task Force; Royal College of Pathologists; Royal College of Physicians; Royal College of Surgeons; European League Against Rheumatism, American College of Rheumatology; FDA; EMA.

A draft search strategy is provided in Appendix 1.

5.2 Assessment structure

This assessment will take the form of two linked systematic reviews.

The first systematic review (Review 1: prognostic factors) will investigate the use of assessment tools and tests in the evaluation of prognosis in early RA patients.

The second systematic review (Review 2: prediction of treatment response) will focus on the ability of selected assessment tools and tests to predict the response to specific treatment. If data allow, treatment will be subdivided into conventional disease modifying anti-rheumatic drugs and biological disease modifying anti-rheumatic drugs.

5.3 Study selection

Results from phase II full searches will be imported into reference management software EndNote (version X7.4, Thompson Reuters) and duplicates removed. Titles and abstracts of search records will be examined and irrelevant evidence excluded. Titles and abstracts will be screened by one reviewer. A randomly selected sample will be checked by a second reviewer. Full texts of remaining articles will be scrutinised for eligibility before inclusion. Study inclusion based on full text articles will be performed by one reviewer and discussed with a second reviewer. Any discrepancies will be resolved by discussion, with involvement of a third team member if required.

Inclusion criteria

A) *Population*

Review 1

Adult patients (aged 18 years and above) diagnosed with early RA. Patients are to have been diagnosed with RA according to established criteria. The definition of early RA will be agreed in consultation with clinical advisors. Studies will be included if they investigate mixed populations only if ≥ 80% of the study population are early RA patients, or if subgroup data are presented for this population.

Review 2

Adult RA patients (aged 18 years and above) who:

i) have received treatment with conventional disease modifying anti-rheumatic drugs / biological disease modifying anti-rheumatic drugs for RA, and

ii) have baseline/early disease and follow-up data for selected tests and assessment tools.

The duration of treatment required for eligibility will be discussed with clinical advisors.

B) Technology

Review 1

Blood tests, imaging modalities, and clinical assessment scores used in the evaluation of prognosis in patients with early RA may be included. Specific tests and assessment tools to be included will be determined following phase I scoping searches and consultation with clinical advisors.

Review 2

Specific tests and assessment tools included in Review 1

Any overlap in technology included in this assessment and HTA TAR 14/16/01 (Ultrasonography for monitoring of synovitis in rheumatoid arthritis) will be considered and noted in the final assessment report.

C) Prognostic and predictive factors

Review 1

Prognostic factors considered in the assessment will be informed by phase I scoping searches and prioritisation of key factors following discussion with clinical advisors, but are likely to include biochemical markers (e.g. Rheumatoid factor, anti-cyclic cittrulinated peptide antibody, C reactive protein [CSR], erythrocyte sedimentation rate [ESR]) and clinical

characteristics (e.g. American College of Rheumatology [ACR] disease activity criteria etc). The potential inclusion of selected patient characteristics will be considered following scoping searches and discussion with clinical advisors.

Review 2

Predictive factors considered in the assessment will be informed by phase I scoping searches and prioritisation following discussion with clinical advisors.

D) Outcomes

Review 1

Selected endpoints considered in this assessment will be informed by discussion with clinical advisors and by those reported in included studies but are likely to include Health Assessment Questionnaire Disability Index (HAQ-DI) progression, disease activity scores, and radiological progression.

Review 2

Response to specific treatment by definitions agreed with clinical advisors. Such endpoints are likely to include Health Assessment Questionnaire Disability Index (HAQ-DI) progression, disease activity scores, and radiological progression.

E) Study types

Review 1

The study types included in Review 1 will be informed by phase I scoping searches but are likely to include published reports of cohort studies. If data from the same study cohort are identified as being reported in multiple articles it is anticipated that only data from the article with the largest cohort will be included (in order to avoid double counting of data). Case-control studies may also be included.

In the event that an unfeasibly large number of primary studies are identified, a pragmatic decision to perform a review of systematic reviews may be made following discussion between the HTA and the assessment team. Other alternatives include i) prioritising specific tests/assessment tools/factors/endpoints to be extracted and analysed, and ii) including the highest methodological quality studies only.

Review 2

Cohort studies and randomised controlled trials (RCTs)

In the event that an unfeasibly large number of primary studies are identified, a pragmatic decision to perform a review of systematic reviews may be made following discussion between the HTA and the assessment team. Other alternatives include i) prioritising specific tests/assessment tools/factors/endpoints to be extracted and analysed, ii) including the highest methodological quality studies only, and iii) including pooled analyses of RCTs.

Exclusion criteria

Primary studies of low methodological quality

Non-English language papers

Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Animal models

Preclinical and biological studies

Narrative reviews, editorials, opinions

5.4 Data extraction strategy

Data will be extracted by one reviewer using a data extraction form piloted on at least two studies (Appendix 2). Extracted data will be checked thoroughly by a second reviewer. Discrepancies will be resolved by discussion, with reference to a third team member if necessary. Data items for extraction are likely to include: study author; year; country; setting; study design; number of patients; method of recruitment; study inclusion criteria; number and reasons for withdrawals; patient characteristics; definitions of prognostic/predictive factors and endpoints; follow-up length; statistical analysis methods; key statistical data (including adjusted and unadjusted associations if provided).

5.5 Quality assessment strategy

It is anticipated that studies will be assessed by criteria informed by the Quality in Prognosis Studies (QUIPS) tool[4] (Appendix 3). It is intended that six domains will be considered: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Items will be scored as high, moderate or low risk of bias. Critical appraisal will be performed by one reviewer and double checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third team member if necessary.

5.6 Methods of analysis/synthesis

Data will be tabulated and discussed separately in the submitted report for i) the association between prognostic factor and disease progression endpoints, and ii) the association between predictive marker and response to treatment. Meta-analyses will be conducted using WinBUGS and R, using a Bayesian random effects model which accounts for between-study heterogeneity in the prognostic/predictive effects. Where appropriate, heterogeneity in prognostic/predictive effects will be explored using meta-regression. Where appropriate, pre-defined subgroup analyses may be performed.

Due to the timescales available for this assessment, the analysis will be restricted to aggregate study level data. It is noted that analysis of individual patient level data (IPD) has several advantages over aggregate level data including harmonisation of risk markers and disease outcomes, the use of consistent approaches to adjustment, and the ability to explore specific combinations of factors. Analysis of IPD would therefore allow a more thorough exploration of the review question. Although it is deemed beyond the scope of the current review, it is anticipated that this assessment will provide background for any potential future in-depth analysis.

6. Report methods for synthesising evidence of cost-effectiveness

As per the commissioning brief for this assessment, this work will not include a cost-effectiveness component.

7. Expertise

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost-effectiveness of healthcare interventions on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE).
A list of publications can be found at:
http://www.sheffield.ac.uk/scharr/sections/heds

Rachel Archer (Research Fellow) has extensive experience in undertaking systematic reviews of clinical effectiveness evidence for health technologies, including NICE single and multiple technology appraisals of pharmacological treatments for rheumatoid arthritis.

Mark Clowes (Information Specialist) has experience of undertaking literature searches for ScHARR-TAG Group systematic reviews and other external projects.

Jean Sanderson (Research Associate) has experience in the application of Bayesian statistics and methods of evidence synthesis for NICE, including single and multiple technology appraisals. She has previously worked on projects evaluating the prognostic ability of novel risk factors (including the EU funded EPIC-CVD project) and has conducted statistical method development in this area.

John Stevens (Reader in Decision Science) has extensive experience in the application of Bayesian statistics and methods of evidence synthesis for NICE (including the multiple technology appraisal of biologic DMARDs in RA), and the National Institute for Health Research (NIHR) Health Technology Assessment programme.

Matt Stevenson (Professor of Health Technology Assessment) is a mathematical modeller and Technical Director of ScHARR-TAG. He led the Assessment Group on the multiple technology appraisal of biologic DMARDs in RA. Matt is a member of NICE Appraisal Committee C and has published in excess of 70 peer-reviewed papers.

Allan Wailoo (Professor of Health Economics) is director of the NICE Decision Support Unit. He has worked on several NICE appraisals of biologic therapies for RA, led a project modelling similar issues in the US for the Agency for HealthCare Research and Quality, won funding to provide health economics support to the development of NICE RA Clinical Guidelines (CG79) and has published several papers on health state utility values in RA.

In addition to the ScHARR-TAG team, two highly experienced RA clinicians have agreed to advise on the assessment and are listed below.

8. Competing interests of authors

ScHARR authors: none

9. Timetable/milestones

Milestone	
Draft protocol	29th January 2016
Final protocol	6th June 2016
Draft assessment report	15th December 2016
Final assessment report	31st January 2017

10. Appendices

Appendix 1 Draft Medline search strategy

Database: Ovid MEDLINE(R) <1946 to January Week 1 2016>

Search Strategy:

Rheumatoid Arthritis synonyms
1 exp rheumatoid arthritis/ (97601)
2 ((rheumatoid or rheumatic) adj2 arthritis).mp. (106586)
3 arthritis deformans.mp. (70)
4 ((rheumatic or rheumatoid) adj2 polyarthritis).mp. (1099)
5 rheumarthritis.mp. (3)
6 1 or 2 or 3 or 4 or 5 (117694)
McMaster sensitivity-maximising filter for identifying prognostic studies
7 incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos*.tw. or predict*.tw. or course*.tw. (2379294)
8 6 and 7 (16000)
Known tests and markers – to expand based on scoping review
9 (disease activity or DAS).mp. (71041)
10 (ESR or erythrocyte sedimentation rate).mp. or Blood Sedimentation/ (25705)
11 C-Reactive Protein/ or c reactive protein*.mp. (50438)
12 ((acr or american college of rheumatology) adj2 (criteri* or score*)).mp. (3181)
13 (ACR20 or ACR 20 or ACR50 or ACR 50 or ACR70 or ACR 70).mp. (831)
14 anti-cyclic citrullinated peptide antibod*.mp. (421)
15 anticyclic citrullinated peptide antibod*.mp. (65)
16 rheumatoid factor*.mp. (12695)
17 exp *Biomarkers/ (265105)
18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (409881)
19 7 or 18 (2699321)
20 6 and 19 (31792)

Appendix 2 Draft data extraction form

Table: Characteristics of included studies

Study details Author, date	**Setting**	**Study design**	**Eligibility criteria, recruitment method**	**Disease and treatment history**	**Sample size and baseline characteristics**	**Technology, description of prognostic/predictive factor**	**Withdrawals (number, reasons, data handling)**

Table: Study outcomes

Study details Author, date	**Joint(s) examined**	**Measurement of prognostic/predictive factor**	**Endpoint measurement, follow-up details**	**Statistical analysis**	**Key findings, statistical data**

Appendix 3 Draft QUIPS quality assessment form

Summary of bias domains of the Quality in Prognosis Studies (QUIPS) tool and optimal study characteristics (adapted from Hayden *et al.*, 2013) [4]

QUIPS bias domains	Optimal study characteristics
1) Study participation	Population of interest is adequately represented by study sample
2) Study attrition	Study sample is adequately represented by available study data
3) Prognostic factor measurement	Prognostic factor is measured consistently across study participants
4) Outcome measurement	Outcome of interest is measured consistently across study participants
5) Study confounding	Key potential confounders are appropriately handled
6) Statistical analysis and reporting	Statistical analysis is appropriate. Primary outcomes are reported.

Domains will be assessed as being at i) high risk of bias, ii) moderate risk of bias, or iii) low risk of bias.

Appendix 4 Description of team members' contributions

TAR team (alphabetical)

Rachel Archer will lead the project and undertake the systematic reviews.

Mark Clowes will be involved in developing the search strategy and undertaking the electronic literature searches.

Gill Rooney will assist in the retrieval of papers and in preparing and formatting the report.

Jean Sanderson and John Stevens will plan, advise on and perform statistical analyses as appropriate.

Matt Stevenson will advise and comment on the assessment throughout.

Allan Wailoo will advise and comment on the assessment throughout.

Clinical advisors

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Clinical specialists will advise and comment on the assessment.

11. References

1. National Collaborating Centre for Chronic Conditions. National Institute for Health and Clinical Excellence: Guidance. In: *Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults* London: Royal College of Physicians (UK); 2009.
2. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* 2009;151:264-9, w64.
3. Geersing GJ, Bouwmeester W, Zuithoff P, Spijker R, Leeflang M, Moons KG. Search filters for finding prognostic and diagnostic prediction studies in Medline to enhance systematic reviews. *PloS One* 2012;7:e32844.
4. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine* 2013;158:280-6.