National Institute for Health and Care Excellence

Consultation

Rheumatoid arthritis in adults: diagnosis and management

Evidence review B Risk factors

Clinical Guideline

Prognostic evidence review

January 2018

Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1 Prognostic factors for poor function

1.1 Review question: In adults with rheumatoid arthritis, which risk factors are associated with poorer long-term function as measured by the Health Assessment Questionnaire (HAQ)?

1.2 Introduction

The 2009 NICE guideline: Rheumatoid arthritis in adults: management CG79 did not specify which people with rheumatoid arthritis (RA) have a poorer prognosis or whether those people should be managed differently from other people with rheumatoid arthritis. The aim of these reviews was to evaluate whether a number of baseline factors are independently associated with poorer long-term outcomes in order to predict prognosis more accurately and inform discussions with people about their prognosis. Specifically, the reviews sought to establish the association between:

- HAQ scores at first presentation, elevated c-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), presence of rheumatoid factor (RF), presence of anti-CCP antibodies or X-ray damage at first presentation, and poorer long-term function as measured by HAQ; and
- elevated CRP, elevated ESR, presence of RF, presence of anti-CCP antibodies or X-ray damage at first presentation, and radiological progression.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults with rheumatoid arthritis
Prognostic variable(s) under consideration	• HAQ scores at first presentation • Elevated levels of CRP • Elevated levels of ESR • Presence or absence of RF • Presence or absence of CCP or ACPA • Presence or absence of X-ray erosion at first presentation • Combinations of these factors (algorithm) All factors should be measured at baseline. People should not be receiving a disease-modifying anti-rheumatic drug (DMARD) treatment at the time of measurement.
Confounding factors	Each of the prognostic variables listed above. Studies that do not consider all of the prognostic variables in the process of conducting a multivariate analysis were excluded.
Outcome(s)	HAQ at 12 months or more
Study design	Prospective cohort studies Systematic reviews of the above

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[10] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for prospective cohort studies and systematic reviews of prognostic cohort studies investigating the association between the following factors: HAQ scores at first presentation, elevated CRP, elevated ESR, presence of RF, presence of CCP or ACPA, or X-ray damage at first presentation, and the outcome of poorer long-term function as measured by the Health Assessment Questionnaire in adults with rheumatoid arthritis.

One study was included in the review; it is summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of prospective cohort studies included in the evidence review

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
Graell 2009[69]	Adults with rheumatoid arthritis recruited from 2 Spanish rheumatology units n=105	Binary multivariate logistic regression	RF+ anti-CCP+ ESR CRP Larsen score Modified Health Assessment Questionnaire (mHAQ) score	All prognostic variables plus an additional 20 variables (see appendix D).	Disability at 2 years (modified HAQ > 0)	Very high risk of bias (outcome cut-off, statistical analysis – methods unclear)

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Poor function

Risk factor for predicting MHAQ > 0 at 2 years	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Baseline RF+	1	Adjusted OR: 3.772 (1.204 – 11.813)	No serious imprecision	LOW
Baseline mHAQ (>0.5)	1	Adjusted OR: 4.023 (1.373 – 11.783)	No serious imprecision	LOW
Baseline mHAQ (continuous)	1	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline anti-CCP+	1	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline ESR	1	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline CRP	1	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline Larsen score	1	Not independently associated with the outcome following multivariable analysis.	n/a	n/a

n/a: unable to assess as data not reported (factor not independently associated with the outcome following multivariable analysis)

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

1.6.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Measuring HAQ score was not recommended in the 2009 guideline and measurement at diagnosis was not reported in a regional survey of guideline implementation published in 2013.[173]

Administration and scoring of HAQ is expected to take 5 minutes of a band-6 nurse or occupational therapist. The unit cost is outlined below.

Table 4: UK costs of measuring HAQ score

Staff	Unit cost per hour	Duration (minutes)(b)	Total cost
Band 6 nurse (a)	£44	5 minutes	£3.67

Source: PSSRU 2016[33]
(a) Unit cost of Band 6 nurse is equivalent to unit cost of band 6 occupational therapist
(b) Committee assumption

1.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

One study reported on the association between the specified risk factors and a mHAQ of greater than 0 at 2 years. The evidence suggested baseline RF positivity was independently associated with a mHAQ of greater than 0 at 2 years. Evidence on the association between baseline mHAQ and mHAQ at 2 years was inconsistent and depended on how the baseline factor was measured. Baseline anti-CCP, ESR, CRP and radiographic damage were not found to be independently associated with mHAQ at 2 years (low quality; n=105).

1.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

For recommendations, rationale and impact and the committee's discussion of the evidence, see sections 2.9, 2.10 and 2.11.

2 Prognostic factors for radiographic progression

2.1 Review question: In adults with rheumatoid arthritis, which risk factors are associated with worse radiographic progression?

2.2 Introduction

The 2009 NICE guideline: Rheumatoid arthritis in adults: management CG79 did not specify which people with rheumatoid arthritis have a poorer prognosis or whether those people should be managed differently from other people with rheumatoid arthritis. The aim of these reviews was to evaluate whether a number of baseline factors are independently associated with poorer long-term outcomes in order to predict prognosis more accurately inform discussions with people about their prognosis. Specifically, the reviews sought to establish the association between:

- HAQ scores at first presentation, elevated c-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), presence of rheumatoid factor (RF), presence of anti-CCP antibodies or X-ray damage at first presentation, and poorer long-term function as measured by HAQ; and
- elevated CRP, elevated ESR, presence of RF, presence of anti-CCP antibodies or X-ray damage at first presentation, and radiological progression.

2.3 PICO table

For full details, see the review protocol in appendix A.

Table 5: PICO characteristics of review question

Population	Adults with rheumatoid arthritis
Prognostic variable(s) under consideration	• Elevated levels of CRP • Elevated levels of ESR • Presence or absence of RF • Presence or absence of CCP/ACPA • Presence or absence of X-ray erosion at first presentation • Combinations of these factors (algorithm) All factors should be measured at baseline. People should not be receiving DMARD treatment at the time of measurement.
Confounding factors	Each of the prognostic variables listed above. Studies that do not consider all of the prognostic variables in the process of conducting a multivariate analysis were excluded.
Outcome(s)	Radiographic progression at 12 months or more
Study design	Prospective cohort studies Systematic reviews of the above

2.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[10] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

2.5 Clinical evidence

2.5.1 Included studies

A search was conducted for prospective cohort studies and systematic reviews of prognostic studies investigating the association between the following factors: elevated CRP, elevated ESR, presence of RF, presence of CCP or ACPA, presence of X-ray damage at first presentation, and the outcome of radiographic progression in adults with rheumatoid arthritis.

Seven studies were included in the review; they are summarised in Table 6 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 7 and Table 8).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

2.5.2 Excluded studies

See the excluded studies list in appendix I.

2.5.3 Summary of clinical studies included in the evidence review

Table 6: Summary of prospective cohort studies included in the evidence review

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcome	Limitations
Audo 2015[4,26]	Adults with rheumatoid arthritis (ESPOIR cohort) recruited from 16 French rheumatology departments n=399	Stepwise multiple logistic regression	RF and ACPA and ESR logCRP level total modified Sharp score	All prognostic variables plus an additional 9 clinical and biomarker variables	Rapid erosion progression at 2 years (change in Sharp erosion score greater than 5)	Very high risk of bias (study participation, study attrition, outcome measurement, statistical analysis)
Courvoisier 2008[32]	Adults with rheumatoid arthritis recruited from 4 French centres n=112	Stepwise multiple logistic regression	anti-CCP+ CRP ESR Immunoglobulin A (IgA) and Immunoglobulin M (IgM) RF+ total Sharp score erosion	All prognostic variables plus an additional 20 clinical and biomarker variables	Above median Sharp score at 10 years	Very high risk of bias (outcome measurement, statistical analysis)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcome	Limitations
			score joint narrowing score			
Forslind 2012[57]	Adults with rheumatoid arthritis recruited from 6 centres in Sweden n=379	Multiple logistic regression	RF+ anti-CCP+ ESR CRP Sharp score presence of erosions	All prognostic variables plus an unspecified number of clinical and biomarker variables at both baseline and 1 year	Radiographic progression at 2 years (Sharp van der Heijde [SvdH] score change of >5.8)	High risk of bias (study attrition) Serious indirectness due to inclusion of variables measured at 1 year in final model.
Güler-Yüksel 2010[72]	Adults with rheumatoid arthritis enrolled in the BeST trial, recruited from 20 hospitals in the Netherlands n=256	Multiple logistic regression	RF+ ACPA+ ESR ≥ 30 mm/h CRP ≥ 10 mg/L SvdH score ≥ 1 unit	All prognostic variables plus an unspecified number of clinical and biomarker variables at both baseline and 1 year. 1-year variables were also adjusted for treatment.	Progressive total joint damage between years 1–4 (≥ 5 units)	Low risk of bias. Serious indirectness due to inclusion of variables measured at 1 year in final model.
Hetland 2009[78]	Adults with rheumatoid arthritis enrolled in the CIMESTRA trial, recruited from 5 rheumatology in Denmark n=130	Multiple linear regression	RF+ anti-CCP+ ESR CRP total Sharp Score (TSS)	All prognostic variables plus an additional 17 demographic, clinical and biomarker variables	Radiographic progression at 2 years (change in TSS)	Low risk of bias
Quintana-Duque 2016[144]	Adults with rheumatoid arthritis recruited from 2 rheumatology units in Columbia n=129	Stepwise multiple logistic regression	RF+ CCP+ ESR CRP presence of erosions SvdH score	All prognostic variables plus an additional 22 demographic, clinical and biomarker variables and a number different of genotypes	Radiographic progression at 3 years (SvdH increase > 3 units)	High risk of bias (study participation)
Sanmarti 2007[157]	Adults with rheumatoid arthritis	Stepwise multiple logistic	RF+ anti-CCP+	All prognostic variables	Radiographic progression	Low risk of bias

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcome	Limitations
	recruited from 2 rheumatology units in Spain n=105	regression	CRP ESR Larsen score	plus an additional 13 clinical and biomarker variables	at 2 years (Larsen score increase >4 units)	Same study population as Graell 2009[69] (included in HAQ outcome review)

1 See appendix D for full evidence tables.

2

2.5.4 Quality assessment of clinical studies included in the evidence review

Table 7: Clinical evidence summary: Radiographic progression (dichotomous – various measures)

Risk factor for predicting radiographic progression	Number of studies[1]	Effect (95% CI)	Imprecision	GRADE Quality
Baseline RF+	1	Adjusted odds ratio (OR): 1.10 (0.38–3.18)	Serious	LOW
	5	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline anti-CCP+	4	Adjusted OR: 3.95 (1.26–12.38) Adjusted OR: 3.48 (1.33–9.07) Adjusted OR: 3.95 (1.17–13.34) Adjusted OR: 3.63 (0.91–14.48)	No serious imprecision	MODERATE
	2	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline ESR	2	Adjusted OR: 1.00 (0.98–1.02) Adjusted OR: 1.04 (1.01–1.08)	No serious imprecision	LOW
	4	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline CRP	1	Adjusted OR: 2.01 (0.83–4.87)	Serious	VERY LOW
	5	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline radiographic damage	4	Adjusted OR: 5.46 (1.78–17.87) Adjusted OR: 0.67 (0.26–1.69) Adjusted OR: 5.87 (1.23–28.02) Adjusted OR: 3.12 (1.23–8.04)	Serious	VERY LOW

Risk factor for predicting radiographic progression	Number of studies[1]	Effect (95% CI)	Imprecision	GRADE Quality
		Adjusted OR: 1.06 (1.01–1.12)[2]		
	2	Not independently associated with the outcome following multivariable analysis	n/a	n/a

[1] All six studies considered all factors in their analyses. Number of studies is the number of studies that provided quantitative results (e.g., adjusted ORs) for that factor, and the number that did not on the basis that the factor was not independently associated with the outcome following multivariable analysis.
[2]Same study as statistic immediately above, investigating continuous rather than dichotomous baseline radiological damage
n/a: unable to assess as data not reported (factor not independently associated with the outcome following multivariable analysis)

Table 8: Clinical evidence summary: Radiographic progression (continuous – change in total Sharp score at 2 years)

Risk factor for predicting radiographic progression	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Baseline RF+	1	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline anti-CCP+	1	Coefficient: 2.94 (-0.1–5.98)	Serious imprecision	MODERATE
Baseline ESR	1	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline CRP	1	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline total Sharp score	1	Coefficient: 0.09 (-0.05–0.22)	Serious imprecision	MODERATE

n/a: unable to assess as data not reported (factor not independently associated with the outcome following multivariable analysis)

See appendix F for full GRADE tables.

2.6 Economic evidence

2.6.1 Included studies

No relevant health economic studies were identified.

2.6.2 Excluded studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

2.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

2.8 Evidence statements

2.8.1 Clinical evidence statements

Seven studies reported on the association between the specified risk factors and radiographic progression. The evidence suggested that baseline ACPA or anti-CCP status (5 of 7 studies, moderate quality evidence, n=1139) and baseline radiographic damage (4 of 7 studies, moderate to very low quality evidence, n=876) were independently associated with radiographic progression at least 12 months later. The evidence was inconsistent with the remaining studies in each case not finding an independent association between the factors and the outcome. Baseline RF+ status (7 of 7 studies, n=1510), ESR level (6 of 7 studies, n=1131) and CRP level (6 of 7 studies, n=1111) were not found to be independently associated with subsequent radiographic progression.

2.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

2.9 Recommendations

B1. As soon as possible after establishing a diagnosis of RA:

- measure anti-CCP antibodies, unless already measured to inform diagnosis
- X-ray the hands and feet to establish whether erosions are present, unless X-rays were performed to inform diagnosis
- measure functional ability using, for example, the Health Assessment Questionnaire (HAQ), to provide a baseline for the assessing the functional response to treatment.

B2. If anti-CCP antibodies are present or there are erosions on X-ray:

- tell the person that they have an increased risk of radiological progression but not necessarily an increased risk of poor function, and
- emphasise the importance of monitoring their condition, and seeking rapid access to specialist care if disease worsens or they have a flare.

2.9.1 Research recommendation

B.RR1. What is the clinical and cost effectiveness of managing RA with a poor prognosis (identified as presence of anti-CCP antibodies or evidence of erosions on X-ray at diagnosis) with a different strategy from that used for standard management of RA?

2.10 Rationale and impact

2.10.1 Why the committee made the recommendations

Evidence showed that anti-cyclic citrullinated peptide (CCP) antibodies and radiographic damage at baseline were both important prognostic factors for subsequent radiographic progression. Anti-CCP antibodies are usually measured and X-rays often taken as part of diagnosis. When this has not been done, the committee agreed that the tests should be performed as soon as possible. The results will inform discussions with the patient about howtheir rheumatoid arthritis (RA) might progress and reinforce the importance of active monitoring and rapidly seeking specialist care if the disease worsens.

There was limited evidence on poor function, as measured by the Health Assessment Questionnaire (HAQ), as a prognostic factor. However, the committee agreed that functional ability (measured, for example, by HAQ) should be determined at diagnosis to provide a baseline for assessing response to treatment at the annual review.

Evidence from the intervention reviews in this updatesuggests that all people with RA should be offered the same therapeutic strategy; however clinical experience of the committee suggested that some people may respond less well and suffer more progressive radiographic damage and impaired function. As evidence was limited as to whether people with poor prognostic markers should follow a different management strategy, and whether a different approach would improve radiographic and functional (HAQ) outcomes in this cohort, the committee agreed that a research recommendation was required.

2.10.2 Why we need recommendations on this topic

The 2009 NICE guideline CG79 did not specify which people with rheumatoid arthritis have a poorer prognosis or whether those people should be managed differently from other people with rheumatoid arthritis. The aim of these reviews was to evaluate whether a number of baseline factors are independently associated with poorer long-term outcomes in order to predict prognosis more accurately inform discussions with people about their prognosis. Specifically, the reviews sought to establish the association between:

- HAQ scores at first presentation, elevated c-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), presence of rheumatoid factor (RF), presence of anti-CCP antibodies or X-ray damage at first presentation, and poorer long-term function as measured by HAQ; and
- elevated CRP, elevated ESR, presence of RF, presence of anti-CCP antibodies or X-ray damage at first presentation, and radiological progression.

2.10.3 Impact of the recommendations on practice

Anti-CCP antibodies are usually measured so there should be no change in current practice. X-raying the hands and feet and measuring functional ability at baseline reflects current best practice, but not everyone with RA currently has these investigations. There may be an increase in the number of X-rays, especially in units without early inflammatory arthritis clinics, but this is unlikely to have a substantial resource impact.

Measuring functional ability at baseline will involve a change of practice for some providers, but the cost is low and so it this is not expected to have a substantial resource impact.

2.11 The committee's discussion of the evidence

2.11.1 Interpreting the evidence

2.11.1.1 The outcomes that matter most

These reviews aimed to identify whether particular baseline factors are associated with poorer long-term outcomes in people with rheumatoid arthritis. The committee agreed that the 2 critical measures of poor long term outcomes were HAQ scores and radiographic progression, both measured at least 12 months after the measurement of the risk factors. Radiographic progression and HAQ are both key measures of progressive disease and disability in people with rheumatoid arthritis.

2.11.1.2 The quality of the evidence

Poor function

Data for poor function measured by HAQ were limited to a single study that considered all of the pre-specified prognostic factors of interest. Evidence for baseline RF+ status and baseline modified HAQ score greater than 0 as independent prognostic factors for modified HAQ at 2 years was considered to be moderate quality as the statistical analysis methods used by the authors were unclear. It was also noted that utilising a cut-off score as an outcome, in this case a modified HAQ score greater than 0, can lead to to people with quite different HAQ scores (anything over 0) applying similar influence on the regression analysis results, further limiting the evidence.

Radiographic progression

Seven studies were identified that considered all of the pre-specified prognostic factors of interest. Evidence for baseline anti-CCP+ status was reported in all 7 studies, but quality could only be assessed in 5 of these and these could not be pooled as the final multivariate models adjusted for different covariates or the methods of measuring radiographic progression or prognostic factor differed. Quality of evidence was affected by various issues including unexplained low study participation and high attrition rates, poor outcome measurement (for example, 1 study dichotomised radiographic progression into 'better' and 'worse' using the median of the study population rather than a clinically meaningful cut-point) and unclear statistical analysis, leading to a rating of moderate quality. Evidence for baseline radiographic damage ranged from very low quality to moderate quality. Baseline RF+ status, ESR level and CRP level similarly ranged from low to very low quality evidence. The majority of the data were considered to be at serious risk of bias for the reasons described above. Inconsistency in the results between studies, concerns about the applicability of the results due to the inclusion of variables measured at 1 year in the author's statistical model, and wide confidence intervals around the effect estimates also affected evidence quality.

Often, where a study found that a variable was not independently associated with the outcome, the authors did not report the impact of the factor on the outcome quantitatively, meaning that the quality of some of the evidence was unable to be fully assessed.

2.11.1.3 Benefits and harms

Poor function

Regarding the review of prognostic factors for subsequent poor function as measured by HAQ, evidence from the single included study suggested that baseline RF+ status is an independent prognostic factor for modified HAQ greater than 0 at 2 years (that is, being RF+ at baseline was associated with [at least some degree of] disability at 2 years). The same study found that a baseline modified HAQ score of greater than 0.5 was also independently

associated with modified HAQ greater than 0 at 2 years. However, the baseline modified HAQ score, as a continuous variable, was not independently associated with the outcome, which raises uncertainty about the true association between baseline HAQ and HAQ at follow-up. The following factors at baseline were also not independently associated with poor function at follow-up: anti-CCP+ status, ESR level, CRP level, or Larsen score.

The committee was not convinced by the limited evidence presented on the prognostic factors for poor function, and did not think it was sufficient to draw any conclusions regarding prognosis. However, the committee noted that the measurement of functional ability (using HAQ or similar) is already recommended in this guideline as part of the annual review. The committee agreed that, without a baseline measure of functional ability, the first assessment of functional ability at the annual review would be of lesser value. Often, people with rheumatoid arthritis have limited function at the time of diagnosis and by performing HAQ at baseline and annually thereafter, change in function following the commencement of drug treatment can be assessed. Baseline HAQ levels may also be useful to identify people who may benefit from non-pharmaceutical management from members of the multidisciplinary team. It is also useful to be aware of HAQ scores at baseline, as the severity of functional disability may not always reflect the level of disease activity (for example, where HAQ score is high but disease activity is low). This may highlight to clinicians that there is some other comorbidity causing the functional impairment, rather than the rheumatoid arthritis itself and enable the referral of people to other services as necessary. In particular, the committee stated that high scores on HAQ are useful as an indicator for clinicians to investigate low mood and depression, as they can be linked to a poor HAQ result. For these reasons, the committee made a consensus recommendation to measure functional ability using HAQ or a similar tool in all people with rheumatoid arthritis following diagnosis.

Radiographic progression

6 of the 7 studies followed people for 2-4 years while one study determined the outcome at 10 years. This study reported results broadly in line with the other studies. Baseline erosions were predictive of radiographic progression however anti-CCP+ status was not found to be.

Evidence from 5 of 7 studies suggested that baseline anti-CCP+ status is independently associated with radiographic progression at least 12 months later. Furthermore, there was also an independent association between baseline radiographic damage and subsequent radiographic progression in 5 of 7 studies. The remaining 2 studies in each case found that the respective risk factors were not independently associated with the outcome.

There was evidence that baseline RF+ status, ESR level and CRP level are not independently associated with subsequent radiographic progression. While there may be a relationship between these factors and subsequent radiographic progression, once anti-CCP+ status and baseline erosions are taken into account, RF+ status, ESR level and CRP level do not have any further impact on the likelihood of radiographic progression. For RF+ status and CRP level, all studies found no independent association; for ESR level, 6 of 7 studies found no independent association. Although baseline RF+ status, ESR level and CRP level were not prognostic factors for subsequent radiographic progression, the committee agreed that it is still important to measure RF+ antibodies and inflammatory markers such as CRP or ESR. RF+ status informs the diagnosis of rheumatoid arthritis, and ESR and CRP are components of key disease activity measures such as DAS (Disease Activity Score), which are used to assess disease severity and monitor response to treatment.

Based on the evidence reviewed, the committee agreed that anti-CCP+ status and radiographic damage at baseline were both important prognostic factors for subsequent radiographic progression. The committee noted that the measurement of anti-CCP antibodies is already included within a recommendation as part of the rheumatoid arthritis diagnostic assessment and that current practice is to measure routinely anti-CCP antibodies in all people with rheumatoid arthritis. X-rays of hands and feet are already recommended as

part of the diagnostic assessment in the case of persistent synovitis, although the committee acknowledged that not all people with rheumatoid arthritis currently receive hand and feet radiographs. The committee considered that a strengthening of the recommendation for people subsequently diagnosed with rheumatoid arthritis (to measure anti-CCP antibodies and take X-rays of hands and feet to confirm erosion status in all people with a diagnosis) was appropriate based on the evidence reviewed.

The committee agreed that identifying people at greater risk of radiographic progression by the measurement of anti-CCP antibodies and baseline erosions was important for informed decision-making. Although the committee did not find evidence in the management evidence reviews to support more intensive management for people with poor prognosis, the committee agreed that aiming for a target of remission (rather than low disease activity) was likely to be even more important in these people, to minimise the risk of disease progression.

The committee also agreed that information about prognosis should be sensitively communicated to the person with rheumatoid arthritis to facilitate their active participation in monitoring of their rheumatoid arthritis. Knowledge of their poor prognosis may encourage the person to be more aware of changes in their symptoms (for example, the recognition of disease flares) and to inform their rheumatologist promptly of these changes so that management can be adjusted accordingly and poor outcomes avoided. In addition the committee agreed that better knowledge and understanding of their prognosis may motivate people with rheumatoid arthritis to adhere to their treatment regimen, especially as people with a poor prognosis may be more likely to eventually require combination therapy and to face the increased risk of side effects associated with a more intensive treatment regimen.

Overall the committee, via consensus, considered that informing the person of their prognosis would aid a collaborative shared care approach, leading to improved outcomes for people with rheumatoid arthritis and minimising unnecessary radiological progression and the associated deterioration of function.

Evidence from the intervention reviews in this updatesuggests that all people with RA should be offered the same therapeutic strategy; however clinical experience of the committee suggested that some people may respond less well and suffer more progressive radiographic damage and impaired function. As evidence was limited as to whether people with poor prognostic markers should follow a different management strategy, and whether a different approach would improve radiographic and functional (HAQ) outcomes in this cohort, the committee agreed that a research recommendation was required

2.11.2 Cost effectiveness and resource use

No health economic studies were identified. As outlined above, measurement of anti-CCP and X-ray are currently recommended as part of diagnostic assessment, although only for a subset of people newly diagnosed with rheumatoid arthritis. In addition, a regional survey of the 2009 NICE guideline implementation (Tugnet 2013) indicated that 82-89% were having anti-CCP measured and 73% were receiving X-rays at diagnosis. The committee considered that strengthening these recommendations to ensure that these are measured at diagnosis for prognostic purposes is unlikely to have a significant impact on current practice. An additional 27% of people newly diagnosed with rheumatoid arthritis would require X-ray, this would be approximately 5,670 additional people (based on an approximate incidence of 21,000 in England[10]). Performing these additional X-rays (2 per person; usually one for both feet and one for both hands) is not considered to have a substantial resource impact based on the £30 unit cost of an individual X-ray published in the 2015-2016 NHS reference costs. [44] Approximately 2,310 to 3,780 additional people will need an anti-CCP test. The cost of measuring anti-CCP is approximately £5 according to the committee. Again, this is not considered to have a substantial resource impact. The committee considered that although there is an additional cost associated with X-ray and measurement of anti-CCP, it is considered an important part of good patient care as it allows healthcare professionals to

inform individuals of their prognosis and therefore ensure they actively monitor their rheumatoid arthritis and understand the importance of medication adherence. The additional costs may also be offset by downstream savings associated with improved and tailored management, for example, in the identification of people who may benefit from non-pharmaceutical treatment.

The committee also noted that the recommendations relating to X-rays are for these to be conducted in specialist care. As a result this may reduce the number of X-rays being conducted in primary care.

The committee found that there was insufficient evidence to support a recommendation of using prognostic factors for subsequent poor function as measured by HAQ. It did note, however, that the measurement of functional ability (using HAQ or similar) is currently recommended at annual review. This measurement, however, is not currently recommended at baseline (diagnosis). The committee agreed that measurement at baseline was important to ensure measurement at annual review was meaningful. This recommendation may lead to a change in practice. The committee discussed the cost of administering and scoring of HAQ. The committee agreed it would take approximately 5 minutes of a band 6 nurse or occupational therapist at a total cost of £3.67 per person. The committee noted that this cost would apply to all people newly diagnosed with rheumatoid arthritis (approximately 21,000 people in England[10]). This additional cost would not have a substantial resource impact and is likely to be offset by downstream savings associated with improved and tailored management, for example, in the identification of people who may benefit from non-pharmaceutical treatment.

2.11.3 Other factors the committee took into account

The lay representatives noted that patient organisations have documented that people with rheumatoid arthritis frequently complain that health professionals do not share the outcomes or explain the meaning of the many tests they have related to their treatment. Healthcare professionals should be aware that shared decision-making, care planning and supported self-management underpin the best outcomes for patients. An explanation of prognostic markers and what they mean for people with rheumatoid arthritis is an important part of this.

References

1. Abhishek A, Doherty M, Kuo CF, Mallen CD, Zhang W, Grainge MJ. Rheumatoid arthritis is getting less frequent-results of a nationwide population-based cohort study. Rheumatology. 2017; 56(5):736-744

2. Ahlmen M, Svensson B, Albertsson K, Forslind K, Hafstrom I, Group BS. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Annals of the Rheumatic Diseases. 2010; 69(1):230-233

3. Andersson ML, Svensson B, Petersson IF, Hafstrom I, Albertsson K, Forslind K et al. Early increase in serum-COMP is associated with joint damage progression over the first five years in patients with rheumatoid arthritis. BMC Musculoskeletal Disorders. 2013; 14:229

4. Audo R, Daien C, Papon L, Lukas C, Vittecoq O, Hahne M et al. Osteoprotegerin and tumor necrosis factor-related apoptosis-inducing ligand as prognostic factors in rheumatoid arthritis: results from the ESPOIR cohort. Arthritis Research & Therapy. 2015; 17:193

5. Baillet A, Gossec L, Paternotte S, Etcheto A, Combe B, Meyer O et al. Evaluation of serum interleukin-6 level as a surrogate marker of synovial inflammation and as a factor of structural progression in early rheumatoid arthritis: results from a French national multicenter cohort. Arthritis Care & Research. 2015; 67(7):905-912

6. Baker JF, Conaghan PG, Emery P, Baker DG, Ostergaard M. Relationship of patient-reported outcomes with MRI measures in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2017; 76(3):486-490

7. Baker JF, Ostergaard M, Emery P, Hsia EC, Lu J, Baker DG et al. Early MRI measures independently predict 1-year and 2-year radiographic progression in rheumatoid arthritis: secondary analysis from a large clinical trial. Annals of the Rheumatic Diseases. 2014; 73(11):1968-1974

8. Balsa A, Del Amo J, Blanco F, Caliz R, Silva L, Sanmarti R et al. Prediction of functional impairment and remission in rheumatoid arthritis patients by biochemical variables and genetic polymorphisms. Rheumatology. 2010; 49(3):458-466

9. Bansback N, Young A, Brennan A, Dixey J. A prognostic model for functional outcome in early rheumatoid arthritis. Journal of Rheumatology. 2006; 33(8):1503-1510

10. Barlow JH, Barefoot J. Group education for people with arthritis. Patient Education and Counseling. 1996; 27(3):257-267

11. Barouta G, Katsiari CG, Alexiou I, Liaskos C, Varna A, Bogdanos DP et al. Anti-MCV antibodies predict radiographic progression in Greek patients with very early (<3 months duration) rheumatoid arthritis. Clinical Rheumatology. 2017; 36(4):885-894

12. Benbouazza K, Benchekroun B, Rkain H, Amine B, Bzami F, Benbrahim L et al. Profile and course of early rheumatoid arthritis in Morocco: a two-year follow-up study. BMC Musculoskeletal Disorders. 2011; 12:266

13. Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Annals of the Rheumatic Diseases. 2006; 65(4):453-458

14. Berglin E, Lorentzon R, Nordmark L, Nilsson-Sojka B, Rantapaa Dahlqvist S. Predictors of radiological progression and changes in hand bone density in early rheumatoid arthritis. Rheumatology. 2003; 42(2):268-275

15. Bjork MA, Thyberg IS, Skogh T, Gerdle BU. Hand function and activity limitation according to health assessment questionnaire in patients with rheumatoid arthritis and healthy referents: 5-year followup of predictors of activity limitation (The Swedish TIRA Project). Journal of Rheumatology. 2007; 34(2):296-302

16. Black RJ, Spargo L, Schultz C, Chatterton B, Cleland L, Lester S et al. Decline in hand bone mineral density indicates increased risk of erosive change in early rheumatoid arthritis. Arthritis Care & Research. 2014; 66(4):515-522

17. Boman A, Kokkonen H, Arlestig L, Berglin E, Rantapaa-Dahlqvist S. Receptor activator of nuclear factor kappa-B ligand (RANKL) but not sclerostin or gene polymorphisms is related to joint destruction in early rheumatoid arthritis. Clinical Rheumatology. 2017; 36(5):1005-1012

18. Bouman CA, den Broeder AA, van der Maas A, van den Hoogen FH, Landewe RB, van Herwaarden N. What causes a small increase in radiographic progression in rheumatoid arthritis patients tapering TNF inhibitors? RMD Open. 2017; 3(1):e000327

19. Boyesen P, Haavardsholm EA, Ostergaard M, van der Heijde D, Sesseng S, Kvien TK. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. Annals of the Rheumatic Diseases. 2011; 70(3):428-433

20. Boyesen P, Haavardsholm EA, Van Der Heijde D, Ostergaard M, Hammer HB, Sesseng S et al. Prediction of MRI erosive progression: A comparison of modern imaging modalities in early rheumatoid arthritis patients. Annals of the Rheumatic Diseases. 2011; 70(1):176-179

21. Boyesen P, Hoff M, Odegard S, Haugeberg G, Syversen SW, Gaarder PI et al. Antibodies to cyclic citrullinated protein and erythrocyte sedimentation rate predict hand bone loss in patients with rheumatoid arthritis of short duration: a longitudinal study. Arthritis Research & Therapy. 2009; 11:R103

22. Breedveld FC, Han C, Bala M, van der Heijde D, Baker D, Kavanaugh AF et al. Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2005; 64(1):52-55

23. Camilleri JP, Amos N, Williams BD, Emery P, Williams LA, Jessop JD. Serum soluble interleukin 2 receptor levels and radiological progression in early rheumatoid arthritis. Journal of Rheumatology. 2001; 28(12):2576-2578

24. Carpenter L, Norton S, Nikiphorou E, Jayakumar K, McWilliams DF, Rennie KL et al. Reductions in radiographic progression in early RA over 25-years: Changing contribution from RF in 2 multi-centre UK inception cohorts. Arthritis Care & Research. 2017; 19:19

25. Chen YC, Su FM, Hsu SW, Chen JF, Cheng TT, Lai HM et al. Predictor of hand radiological progression in patients with rheumatoid arthritis receiving TNF antagonist therapy by change in grayscale synovitis-a preliminary study. Journal of Clinical Rheumatology. 2017; 23(2):73-76

26. Combe B, Benessiano J, Berenbaum F, Cantagrel A, Daures JP, Dougados M et al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology

and baseline characteristics of the 813 included patients. Joint, Bone, Spine: Revue du Rhumatisme. 2007; 74(5):440-445

27. Combe B, Cantagrel A, Goupille P, Bozonnat MC, Sibilia J, Eliaou JF et al. Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. Journal of Rheumatology. 2003; 30(11):2344-2349

28. Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis & Rheumatism. 2001; 44(8):1736-1743

29. Combe B, Rincheval N, Benessiano J, Berenbaum F, Cantagrel A, Daures JP et al. Five-year favorable outcome of patients with early rheumatoid arthritis in the 2000s: data from the ESPOIR cohort. Journal of Rheumatology. 2013; 40(10):1650-1657

30. Contreras-Yanez I, Rull-Gabayet M, Vazquez-Lamadrid J, Pascual-Ramos V. Radiographic outcome in Hispanic early rheumatoid arthritis patients treated with conventional disease modifying anti-rheumatic drugs. European Journal of Radiology. 2011; 79(2):e52-57

31. Coste J, Spira A, Clerc D, Paolaggi JB. Prediction of articular destruction in rheumatoid arthritis: disease activity markers revisited. Journal of Rheumatology. 1997; 24(1):28-34

32. Courvoisier N, Dougados M, Cantagrel A, Goupille P, Meyer O, Sibilia J et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Research & Therapy. 2008; 10:R106

33. Curtis L, Burns A. Unit costs of health and social care 2016. Canterbury. Personal Social Services Research Unit University of Kent, 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/

34. da Mota LM, Dos Santos Neto LL, de Carvalho JF, Pereira IA, Burlingame R, Menard HA et al. The presence of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor on patients with rheumatoid arthritis (RA) does not interfere with the chance of clinical remission in a follow-up of 3 years. Rheumatology International. 2012; 32(12):3807-3812

35. da Mota LM, Dos Santos Neto LL, Oliveira AC, Pereira IA, Burlingame RW, Menard HA et al. Baseline HAQ and SF-36 questionnaire scores cannot predict clinical remission, radiographic progression or the need for biological therapy in a three-year prospective study of a Brazilian early rheumatoid arthritis cohort. Rheumatology International. 2012; 32(12):3937-3943

36. Davis ML, LeVan TD, Yu F, Sayles H, Sokolove J, Robinson W et al. Associations of toll-like receptor (TLR)-4 single nucleotide polymorphisms and rheumatoid arthritis disease progression: an observational cohort study. International Immunopharmacology. 2015; 24(2):346-352

37. De Cock D, Vanderschueren G, Meyfroidt S, Joly J, Van der Elst K, Westhovens R et al. The performance of matrices in daily clinical practice to predict rapid radiologic progression in patients with early RA. Seminars in Arthritis and Rheumatism. 2014; 43(5):627-631

38. de Miguel E, Pecondon-Espanol A, Castano-Sanchez M, Corrales A, Gutierrez-Polo R, Rodriguez-Gomez M et al. A reduced 12-joint ultrasound examination predicts lack of X-ray progression better than clinical remission criteria in patients with rheumatoid arthritis. Rheumatology International. 2017; 07:07

39. de Punder YM, van Riel PL, Fransen J. A simplified baseline prediction model for joint damage progression in rheumatoid arthritis: a step toward personalized medicine. Journal of Rheumatology. 2015; 42(3):391-397

40. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis & Rheumatism. 2008; 58(5):1293-1298

41. Degboe Y, Constantin A, Nigon D, Tobon G, Cornillet M, Schaeverbeke T et al. Predictive value of autoantibodies from anti-CCP2, anti-MCV and anti-human citrullinated fibrinogen tests, in early rheumatoid arthritis patients with rapid radiographic progression at 1 year: results from the ESPOIR cohort. RMD Open. 2015; 1(1):e000180

42. Deighton CM, Surtees D, Walker DJ. Influence of the severity of rheumatoid arthritis on sex differences in health assessment questionnaire scores. Annals of the Rheumatic Diseases. 1992; 51(4):473-475

43. den Broeder AA, Joosten LA, Saxne T, Heinegard D, Fenner H, Miltenburg AM et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. Annals of the Rheumatic Diseases. 2002; 61(4):311-318

44. Department of Health. NHS reference costs 2015-16. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016 Last accessed: 06/10/2017.

45. Dixey J, Solymossy C, Young A, Early RAS. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). Journal of Rheumatology - Supplement. 2004; 69:48-54

46. Dohn UM, Ejbjerg B, Boonen A, Hetland ML, Hansen MS, Knudsen LS et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. Annals of the Rheumatic Diseases. 2011; 70(2):252-258

47. Drossaers-Bakker KW, Zwinderman AH, Vliet Vlieland TP, Van Zeben D, Vos K, Breedveld FC et al. Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year followup. Arthritis & Rheumatism. 2002; 47(4):383-390

48. Drouin J, Haraoui B, 3e Initiative Group. Predictors of clinical response and radiographic progression in patients with rheumatoid arthritis treated with methotrexate monotherapy. Journal of Rheumatology. 2010; 37(7):1405-1410

49. Eberhardt KB, Fex E. Functional impairment and disability in early rheumatoid arthritis--development over 5 years. Journal of Rheumatology. 1995; 22(6):1037-1042

50. Ellingsen T, Hansen I, Thorsen J, Moller BK, Tarp U, Lottenburger T et al. Upregulated baseline plasma CCL19 and CCR7 cell-surface expression on monocytes in early rheumatoid arthritis normalized during treatment and CCL19 correlated with radiographic progression. Scandinavian Journal of Rheumatology. 2014; 43(2):91-100

51. Euesden J, Matcham F, Hotopf M, Steer S, Cope AP, Lewis CM et al. The Relationship Between Mental Health, Disease Severity, and Genetic Risk for Depression in Early Rheumatoid Arthritis. Psychosomatic Medicine. 2017; 79(6):638-645

52. Fautrel B, Nab HW, Brault Y, Gallo G. Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment. RMD Open. 2015; 1(1):e000018

53. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. British Journal of Rheumatology. 1996; 35(11):1106-1115

54. Fisher BA, Plant D, Brode M, van Vollenhoven RF, Mathsson L, Symmons D et al. Antibodies to citrullinated alpha-enolase peptide 1 and clinical and radiological outcomes in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2011; 70(6):1095-1098

55. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B, Barfot Study Group. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Annals of the Rheumatic Diseases. 2004; 63(9):1090-1095

56. Forslind K, Boonen A, Albertsson K, Hafstrom I, Svensson B, Barfot Study Group. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2009; 38(6):431-438

57. Forslind K, Kalvesten J, Hafstrom I, Svensson B, Barfot Study Group. Does digital X-ray radiogrammetry have a role in identifying patients at increased risk for joint destruction in early rheumatoid arthritis? Arthritis Research & Therapy. 2012; 14:R219

58. Forslind K, Keller C, Svensson B, Hafstrom I, Barfot Study Group. Reduced bone mineral density in early rheumatoid arthritis is associated with radiological joint damage at baseline and after 2 years in women. Journal of Rheumatology. 2003; 30(12):2590-2596

59. Forslind K, Larsson EM, Eberhardt K, Johansson A, Svensson B. Magnetic resonance imaging of the knee: a tool for prediction of joint damage in early rheumatoid arthritis? Scandinavian Journal of Rheumatology. 2004; 33(3):154-161

60. Forslind K, Vincent C, Serre G, Svensson B. Antifilaggrin antibodies in early rheumatoid arthritis may predict radiological progression. Scandinavian Journal of Rheumatology. 2001; 30(4):221-224

61. Funck-Brentano T, Gandjbakhch F, Etchepare F, Jousse-Joulin S, Miquel A, Cyteval C et al. Prediction of radiographic damage in early arthritis by sonographic erosions and power Doppler signal: a longitudinal observational study. Arthritis Care & Research. 2013; 65(6):896-902

62. Galil SM, El-Shafey AM, Hagrass HA, Fawzy F, Sammak AE. Baseline serum level of matrix metalloproteinase-3 as a biomarker of progressive joint damage in rheumatoid arthritis patients. International Journal of Rheumatic Diseases. 2016; 19(4):377-384

63. Gandjbakhch F, Haavardsholm EA, Conaghan PG, Ejbjerg B, Foltz V, Brown AK et al. Determining a magnetic resonance imaging inflammatory activity acceptable state without subsequent radiographic progression in rheumatoid arthritis: results from a

followup MRI study of 254 patients in clinical remission or low disease activity. Journal of Rheumatology. 2014; 41(2):398-406

64. Garnero P, Landewe R, Boers M, Verhoeven A, Van Der Linden S, Christgau S et al. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. Arthritis & Rheumatism. 2002; 46(11):2847-2856

65. Garnero P, Tabassi NC, Voorzanger-Rousselot N. Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with etanercept. Journal of Rheumatology. 2008; 35(12):2313-2315

66. Glinatsi D, Baker JF, Hetland ML, Horslev-Petersen K, Ejbjerg BJ, Stengaard-Pedersen K et al. Magnetic resonance imaging assessed inflammation in the wrist is associated with patient-reported physical impairment, global assessment of disease activity and pain in early rheumatoid arthritis: longitudinal results from two randomised controlled trials. Annals of the Rheumatic Diseases. 2017; 13:13

67. Gomez-Vaquero C, Martin I, Loza E, Carmona L, Ivorra J, Narvaez JA et al. Effect of osteoprotegerin and Dickkopf-related protein 1 on radiological progression in tightly controlled rheumatoid arthritis. PloS One. 2016; 11(12):e0166691

68. Goronzy JJ, Matteson EL, Fulbright JW, Warrington KJ, Chang-Miller A, Hunder GG et al. Prognostic markers of radiographic progression in early rheumatoid arthritis. Arthritis & Rheumatism. 2004; 50(1):43-54

69. Graell E, Vazquez I, Larrosa M, Rodriguez-Cros JR, Hernandez MV, Gratacos J et al. Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: prognostic factors after two years of follow-up. Clinical and Experimental Rheumatology. 2009; 27(2):284-291

70. Grandaunet B, Syversen SW, Hoff M, Sundan A, Haugeberg G, van Der Heijde D et al. Association between high plasma levels of hepatocyte growth factor and progression of radiographic damage in the joints of patients with rheumatoid arthritis. Arthritis & Rheumatism. 2011; 63(3):662-669

71. Guillemin F, Gerard N, van Leeuwen M, Smedstad LM, Kvien TK, van den Heuvel W et al. Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. Journal of Rheumatology. 2003; 30(12):2585-2589

72. Guler-Yuksel M, Klarenbeek NB, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van der Kooij SM, Gerards AH et al. Accelerated hand bone mineral density loss is associated with progressive joint damage in hands and feet in recent-onset rheumatoid arthritis. Arthritis Research & Therapy. 2010; 12:R96

73. Hambardzumyan K, Bolce R, Saevarsdottir S, Cruickshank SE, Sasso EH, Chernoff D et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Annals of the Rheumatic Diseases. 2015; 74(6):1102-1109

74. Hambardzumyan K, Bolce RJ, Saevarsdottir S, Forslind K, Wallman JK, Cruickshank SE et al. Association of a multibiomarker disease activity score at multiple time-points with radiographic progression in rheumatoid arthritis: results from the SWEFOT trial. RMD Open. 2016; 2(1):e000197

75. Hammer HB, Odegard S, Syversen SW, Landewe R, van der Heijde D, Uhlig T et al. Calprotectin (a major S100 leucocyte protein) predicts 10-year radiographic progression in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010; 69(1):150-154

76. Harvey S, Whaley J, Eberhardt K. The relationship between serum levels of YKL-40 and disease progression in patients with early rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2000; 29(6):391-393

77. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Modern Rheumatology. 2009; 19(3):273-282

78. Hetland ML, Ejbjerg B, Horslev-Petersen K, Jacobsen S, Vestergaard A, Jurik AG et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). Annals of the Rheumatic Diseases. 2009; 68(3):384-390

79. Hetland ML, Stengaard-Pedersen K, Junker P, Ostergaard M, Ejbjerg BJ, Jacobsen S et al. Radiographic progression and remission rates in early rheumatoid arthritis - MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Annals of the Rheumatic Diseases. 2010; 69(10):1789-1795

80. Hoff M, Haugeberg G, Odegard S, Syversen S, Landewe R, van der Heijde D et al. Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. Annals of the Rheumatic Diseases. 2009; 68(3):324-329

81. Hoff M, Kvien TK, Kalvesten J, Elden A, Haugeberg G. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Annals of the Rheumatic Diseases. 2009; 68(7):1171-1176

82. Humphreys J, Verheul M, Barton A, Fu B, Toes R, Symmons D et al. Association of anti-carbamylated protein antibodies with long-term disability and increased disease activity in patients with early inflammatory arthritis: results from the Norfolk Arthritis Register. Lancet. 2015; 385 (Suppl 1):S44

83. Humphreys JH, Verstappen SM, Hyrich KL, Chipping JR, Marshall T, Symmons DP. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the Rheumatic Diseases. 2013; 72(8):1315-1320

84. Innala L, Kokkonen H, Eriksson C, Jidell E, Berglin E, Dahlqvst SR. Antibodies against mutated citrullinated vimentin are a better predictor of disease activity at 24 months in early rheumatoid arthritis than antibodies against cyclic citrullinated peptides. Journal of Rheumatology. 2008; 35(6):1002-1008

85. Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2001; 60(10):924-927

86. Jantti JK, Kaarela K, Luukkainen RK, Kautiainen HJ. Prediction of 20-year outcome at onset of seropositive rheumatoid arthritis. Clinical and Experimental Rheumatology. 2000; 18(3):387-390

87. Jawaheer D, Maranian P, Park G, Lahiff M, Amjadi SS, Paulus HE. Disease progression and treatment responses in a prospective DMARD-naive seropositive early rheumatoid arthritis cohort: does gender matter? Journal of Rheumatology. 2010; 37(12):2475-2485

88. Joo YB, Bang SY, Ryu JA, Lee S, Lee HS, Bae SC. Predictors of severe radiographic progression in patients with early rheumatoid arthritis: Prospective observational cohort study. International Journal of Rheumatic Diseases. 2017; 05:05

89. Kaltenhauser S, Pierer M, Arnold S, Kamprad M, Baerwald C, Hantzschel H et al. Antibodies against cyclic citrullinated peptide are associated with the DRB1 shared epitope and predict joint erosion in rheumatoid arthritis. Rheumatology. 2007; 46(1):100-104

90. Kaltenhauser S, Wagner U, Schuster E, Wassmuth R, Arnold S, Seidel W et al. Immunogenetic markers and seropositivity predict radiological progression in early rheumatoid arthritis independent of disease activity. Journal of Rheumatology. 2001; 28(4):735-744

91. Kapetanovic MC, Lindqvist E, Nilsson JA, Geborek P, Saxne T, Eberhardt K. Development of functional impairment and disability in rheumatoid arthritis patients followed for 20 years: relation to disease activity, joint damage, and comorbidity. Arthritis Care & Research. 2015; 67(3):340-348

92. Karlson EW, Chibnik LB, Cui J, Plenge RM, Glass RJ, Maher NE et al. Associations between human leukocyte antigen, PTPN22, CTLA4 genotypes and rheumatoid arthritis phenotypes of autoantibody status, age at diagnosis and erosions in a large cohort study. Annals of the Rheumatic Diseases. 2008; 67(3):358-363

93. Karpouzas GA, Draper T, Moran R, Hernandez E, Nicassio P, Weisman MH et al. Trends in Functional Disability and Determinants of Clinically Meaningful Change Over Time in Hispanic Patients With Rheumatoid Arthritis in the US. Arthritis Care & Research. 2017; 69(2):294-298

94. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Annals of the Rheumatic Diseases. 2004; 63(9):1085-1089

95. Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. Relation between body mass index and radiological progression in patients with rheumatoid arthritis. Journal of Rheumatology. 2003; 30(11):2350-2355

96. Khanna D, Ranganath VK, Fitzgerald J, Park GS, Altman RD, Elashoff D et al. Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage. Arthritis & Rheumatism. 2005; 52(8):2284-2292

97. Koga T, Okada A, Fukuda T, Hidaka T, Ishii T, Ueki Y et al. Prognostic factors toward clinically relevant radiographic progression in patients with rheumatoid arthritis in clinical practice: a Japanese multicenter, prospective longitudinal cohort study for achieving a treat-to-target strategy. Medicine. 2016; 95(17):e3476

98. Koga T, Okada A, Fukuda T, Hidaka T, Ishii T, Ueki Y et al. Anti-citrullinated peptide antibodies are the strongest predictor of clinically relevant radiographic progression in rheumatoid arthritis patients achieving remission or low disease activity: A post hoc analysis of a nationwide cohort in Japan. PLoS ONE [Electronic Resource]. 2017; 12(5):e0175281

99. Kondo Y, Kaneko Y, Sugiura H, Matsumoto S, Nishina N, Kuwana M et al. Pre-treatment interleukin-6 levels strongly affect bone erosion progression and repair detected by magnetic resonance imaging in rheumatoid arthritis patients. Rheumatology. 2017; 08:08

100. Krabben A, Huizinga TW, Mil AH. Biomarkers for radiographic progression in rheumatoid arthritis. Current Pharmaceutical Design. 2015; 21(2):147-169

101. Kroot EJ, de Jong BA, van Leeuwen MA, Swinkels H, van den Hoogen FH, van't Hof M et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis & Rheumatism. 2000; 43(8):1831-1835

102. Kuru O, Bilgici A, Birinci A, Ulusoy H, Durupinar B. Prognostic value of anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. Bratislavske Lekarske Listy. 2009; 110(10):650-654

103. Lee YC, Cui J, Lu B, Frits ML, Iannaccone CK, Shadick NA et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. Arthritis Research & Therapy. 2011; 13(3):R83

104. Leigh JP, Fries JF. Predictors of disability in a longitudinal sample of patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 1992; 51(5):581-587

105. Liao KP, Weinblatt ME, Cui J, Iannaccone C, Chibnik LB, Lu B et al. Clinical predictors of erosion-free status in rheumatoid arthritis: a prospective cohort study. Rheumatology. 2011; 50(8):1473-1479

106. Lin L, Xiao Z, Huang S, Xu J. Analysis of correlative factors on prognosis in rheumatoid arthritis. Chinese Journal of Clinical Rehabilitation. 2003; 7(12):1796-1797

107. Lindqvist E, Eberhardt K, Bendtzen K, Heinegard D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2005; 64(2):196-201

108. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2003; 62(7):611-616

109. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Annals of the Rheumatic Diseases. 2002; 61(12):1055-1059

110. Linn-Rasker SP, van der Helm-van Mil AHM, Breedveld FC, Huizinga TW. Arthritis of the large joints - in particular, the knee - at first presentation is predictive for a high level of radiological destruction of the small joints in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007; 66(5):646-650

111. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology. 2007; 46(2):342-349

112. Maillefert JF, Combe B, Goupille P, Cantagrel A, Dougados M. The 5-yr HAQ-disability is related to the first year's changes in the narrowing, rather than erosion score in patients with recent-onset rheumatoid arthritis. Rheumatology. 2004; 43(1):79-84

113. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M et al. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. Rheumatology. 2006; 45(6):734-740

114. Manivel VA, Mullazehi M, Padyukov L, Westerlind H, Klareskog L, Alfredsson L et al. Anticollagen type II antibodies are associated with an acute onset rheumatoid arthritis phenotype and prognosticate lower degree of inflammation during 5 years follow-up. Annals of the Rheumatic Diseases. 2017; 23:23

115. Mathsson L, Mullazehi M, Wick MC, Sjoberg O, van Vollenhoven R, Klareskog L et al. Antibodies against citrullinated vimentin in rheumatoid arthritis: higher sensitivity and extended prognostic value concerning future radiographic progression as compared with antibodies against cyclic citrullinated peptides. Arthritis & Rheumatism. 2008; 58(1):36-45

116. Matsushita I, Motomura H, Seki E, Kimura T. Radiographic changes and factors associated with subsequent progression of damage in weight-bearing joints of patients with rheumatoid arthritis under TNF-blocking therapies-three-year observational study. Modern Rheumatology. 2017; 27(4):570-575

117. McQueen FM, Benton N, Perry D, Crabbe J, Robinson E, Yeoman S et al. Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2003; 48(7):1814-1827

118. Mewar D, Coote A, Moore DJ, Marinou I, Keyworth J, Dickson MC et al. Independent associations of anti-cyclic citrullinated peptide antibodies and rheumatoid factor with radiographic severity of rheumatoid arthritis. Arthritis Research & Therapy. 2006; 8(4):R128

119. Meyer O, Labarre C, Dougados M, Goupille P, Cantagrel A, Dubois A et al. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. Annals of the Rheumatic Diseases. 2003; 62(2):120-126

120. Meyer O, Nicaise-Roland P, Santos MD, Labarre C, Dougados M, Goupille P et al. Serial determination of cyclic citrullinated peptide autoantibodies predicted five-year radiological outcomes in a prospective cohort of patients with early rheumatoid arthritis. Arthritis Research & Therapy. 2006; 8:R40

121. Michaud K, Wallenstein G, Wolfe F. Treatment and nontreatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. Arthritis Care & Research. 2011; 63(3):366-372

122. Miriovsky BJ, Michaud K, Thiele GM, O'Dell JR, Cannon GW, Kerr G et al. Anti-CCP antibody and rheumatoid factor concentrations predict greater disease activity in men with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010; 69(7):1292-1297

123. Mohammed RH, Farahat F, Kewan HH, Bukhari MA. Predictors of European League Against Rheumatism (EULAR) good response, DAS-28 remission and sustained responses to TNF-inhibitors in rheumatoid arthritis: a prospective study in refractory disease. Springerplus. 2015; 4:207

124. Nakajima A, Aoki Y, Sonobe M, Takahashi H, Saito M, Terayama K et al. Radiographic progression of large joint damage in patients with rheumatoid arthritis treated with biological disease-modifying anti-rheumatic drugs. Modern Rheumatology. 2016; 26(4):517-521

125. Nakajima A, Aoki Y, Terayama K, Sonobe M, Takahashi H, Saito M et al. Health assessment questionnaire-disability index (HAQ-DI) score at the start of biological disease-modifying antirheumatic drug (bDMARD) therapy is associated with radiographic progression of large joint damage in patients with rheumatoid arthritis. Modern Rheumatology. 2017:1-6

126. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

127. Navarro-Compan V, Landewe R, Provan SA, Odegard S, Uhlig T, Kvien TK et al. Relationship between types of radiographic damage and disability in patients with rheumatoid arthritis in the EURIDISS cohort: a longitudinal study. Rheumatology. 2015; 54(1):83-90

128. Nawata M, Saito K, Fukuyo S, Hirata S, Tanaka Y. Clinically relevant radiographic progression in joint destruction in RA patients with abnormal MMP-3 or high levels of CRP despite 1-year treatment with infliximab. Modern Rheumatology. 2016; 26(6):807-812

129. Nieto-Colonia AM, Santos WS, Keusseyan SP, Caldana W, Fernandes AR, Andrade LE. Antibodies to citrullinated peptides are not associated with the rate of joint destruction in patients with a well-established diagnosis of rheumatoid arthritis. Brazilian Journal of Medical and Biological Research. 2008; 41(3):188-192

130. Nissen MJ, Gabay C, Scherer A, Finckh A, Swiss Clinical Quality Management Project in Rheumatoid A. The effect of alcohol on radiographic progression in rheumatoid arthritis. Arthritis & Rheumatism. 2010; 62(5):1265-1272

131. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Seminars in Arthritis and Rheumatism. 2014; 44(2):131-144

132. Odegard S, Landewe R, van der Heijde D, Kvien TK, Mowinckel P, Uhlig T. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients. Arthritis & Rheumatism. 2006; 54(1):68-75

133. Office for National Statistics. Population estimates. 2015. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates Last accessed: 13/11/2017.

134. Ornbjerg LM, Ostergaard M, Boyesen P, Krogh NS, Thormann A, Tarp U et al. Which factors influence radiographic progression during treatment with tumor necrosis factor inhibitors in clinical practice? Results from 930 patients with rheumatoid arthritis in the nationwide Danish DANBIO registry. Journal of Rheumatology. 2014; 41(12):2352-2360

135. Ornbjerg LM, Ostergaard M, Jensen T, Horslev-Petersen K, Stengaard-Pedersen K, Junker P et al. Hand bone loss in early rheumatoid arthritis during a methotrexate-based treat-to-target strategy with or without adalimumab-a substudy of the optimized treatment algorithm in early RA (OPERA) trial. Clinical Rheumatology. 2017; 36(4):781-789

136. Paimela L, Palosuo T, Leirisalo-Repo M, Helve T, Aho K. Prognostic value of quantitative measurement of rheumatoid factor in early rheumatoid arthritis. British Journal of Rheumatology. 1995; 34(12):1146-1150

137. Park GS, Wong WK, Elashoff DA, Khanna D, Gold RH, Paulus HE. Patterns of radiographic outcomes in early, seropositive rheumatoid arthritis: a baseline analysis. Contemporary Clinical Trials. 2011; 32(2):160-168

138. Park YJ, Yoo SA, Kim GR, Cho CS, Kim WU. Urinary interleukin-6 as a predictor of radiographic progression in rheumatoid arthritis: A 3-year evaluation. Scientific Reports. 2016; 6:35242

139. Pascual-Ramos V, Contreras-Yanez I, Cabiedes-Contreras J, Rull-Gabayet M, Villa AR, Vazquez-Lamadrid J et al. Hypervascular synovitis and American College of Rheumatology Classification Criteria as predictors of radiographic damage in early rheumatoid arthritis. Ultrasound Quarterly. 2009; 25(1):31-38

140. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. Rheumatology. 1999; 38(3):228-234

141. Plant D, Thomson W, Lunt M, Flynn E, Martin P, Eyre S et al. The role of rheumatoid arthritis genetic susceptibility markers in the prediction of erosive disease in patients with early inflammatory polyarthritis: results from the Norfolk Arthritis Register. Rheumatology. 2011; 50(1):78-84

142. Prodanovic SZ, Radunovic G, Sefic-Bukilica M, Seric S, Damjanov N. The importance of biomarkers (RF, ACPA and MMP-3) serum levels of rheumatoid arthritis (RA) in prediction bone erosions in patients with early RA and no visible radiographic structural damages-an echosonographic study. Annals of the Rheumatic Diseases. 2016; 75(Suppl 2):981

143. Quinn MA, Gough AK, Green MJ, Devlin J, Hensor EM, Greenstein A et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. Rheumatology. 2006; 45(4):478-480

144. Quintana-Duque MA, Rondon-Herrera F, Mantilla RD, Calvo-Paramo E, Yunis JJ, Varela-Narino A et al. Predictors of remission, erosive disease and radiographic progression in a Colombian cohort of early onset rheumatoid arthritis: a 3-year follow-up study. Clinical Rheumatology. 2016; 35(6):1463-1473

145. Ranganath VK, Paulus HE, Onofrei A, Khanna D, Reed G, Elashoff DA et al. Functional improvement after patients with rheumatoid arthritis start a new disease modifying antirheumatic drug (DMARD) associated with frequent changes in DMARD: the CORRONA database. Journal of Rheumatology. 2008; 35(10):1966-1971

146. Reeback J, Silman A. Predictors of outcome at two years in patients with rheumatoid arthritis. Journal of the Royal Society of Medicine. 1984; 77(12):1002-1005

147. Reneses S, Gonzalez-Escribano MF, Fernandez-Suarez A, Pestana L, Davila B, Wichmann I et al. The value of HLA-DRB1 shared epitope, -308 tumor necrosis factor-alpha gene promoter polymorphism, rheumatoid factor, anti-citrullinated peptide antibodies, and early erosions for predicting radiological outcome in recent-onset rheumatoid arthritis. Journal of Rheumatology. 2009; 36(6):1143-1149

148. Richi P, Balsa A, Munoz-Fernandez S, Villaverde V, Fernandez-Prada M, Vicario JL et al. Factors related to radiological damage in 61 Spaniards with early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2002; 61(3):270-272

149. Rojas-Villarraga A, Diaz FJ, Calvo-Paramo E, Salazar JC, Iglesias-Gamarra A, Mantilla RD et al. Familial disease, the HLA-DRB1 shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis. Journal of Autoimmunity. 2009; 32(1):64-69

150. Ronnelid J, Wick MC, Lampa J, Lindblad S, Nordmark B, Klareskog L et al. Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity

and greater radiological progression. Annals of the Rheumatic Diseases. 2005; 64(12):1744-1749

151. Rooney T, Edwards CK, 3rd, Gogarty M, Greenan L, Veale DJ, FitzGerald O et al. Synovial tissue rank ligand expression and radiographic progression in rheumatoid arthritis: observations from a proof-of-concept randomized clinical trial of cytokine blockade. Rheumatology International. 2010; 30(12):1571-1580

152. Rupp I, Boshuizen HC, Dinant HJ, Jacobi CE, van den Bos GA. Disability and health-related quality of life among patients with rheumatoid arthritis: association with radiographic joint damage, disease activity, pain, and depressive symptoms. Scandinavian Journal of Rheumatology. 2006; 35(3):175-181

153. Ruyssen-Witrand A, Guernec G, Nigon D, Tobon G, Jamard B, Rat AC et al. Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes. Annals of the Rheumatic Diseases. 2015; 74(9):1676-1683

154. Saeki Y, Kudo-Tanaka E, Ohshima S, Matsushita M, Tsuji S, Maeda Y et al. Baseline anti-citrullinated peptide antibody (ACPA) titers and serum interleukin-6 (IL-6) levels possibly predict progression of bone destruction in early stages of rheumatoid arthritis (ERA). Rheumatology International. 2013; 33(2):451-456

155. Saevarsdottir S, Rezaei H, Geborek P, Petersson I, Ernestam S, Albertsson K et al. Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial. Annals of the Rheumatic Diseases. 2015; 74(8):1509-1514

156. Salaffi F, Carotti M, Ciapetti A, Gasparini S, Filippucci E, Grassi W. Relationship between time-integrated disease activity estimated by DAS28-CRP and radiographic progression of anatomical damage in patients with early rheumatoid arthritis. BMC Musculoskeletal Disorders. 2011; 12:120

157. Sanmarti R, Gomez-Centeno A, Ercilla G, Larrosa M, Vinas O, Vazquez I et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clinical Rheumatology. 2007; 26(7):1111-1118

158. Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Suris X et al. Radiological progression in early rheumatoid arthritis after DMARDS: a one-year follow-up study in a clinical setting. Rheumatology. 2003; 42(9):1044-1049

159. Sanmarti R, Graell E, Perez ML, Ercilla G, Vinas O, Gomez-Puerta JA et al. Diagnostic and prognostic value of antibodies against chimeric fibrin/filaggrin citrullinated synthetic peptides in rheumatoid arthritis. Arthritis Research & Therapy. 2009; 11(5):R135

160. Sherrer YS, Bloch DA, Mitchell DM, Young DY, Fries JF. The development of disability in rheumatoid arthritis. Arthritis & Rheumatism. 1986; 29(4):494-500

161. Shi J, Knevel R, Suwannalai P, van der Linden MP, Janssen GM, van Veelen PA et al. Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108(42):17372-17377

162. Smolen JS, Van Der Heijde DM, St Clair EW, Emery P, Bathon JM, Keystone E et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis & Rheumatism. 2006; 54(3):702-710

163. Soderlin MK, Bergman S, Group BS. Absent "Window of Opportunity" in smokers with short disease duration. Data from BARFOT, a multicenter study of early rheumatoid arthritis. Journal of Rheumatology. 2011; 38(10):2160-2168

164. Stockman A, Emery P, Doyle T, Hopper J, Tait B, Muirden K. Relationship of progression of radiographic changes in hands and wrists, clinical features and HLA-DR antigens in rheumatoid arthritis. Journal of Rheumatology. 1991; 18(7):1001-1007

165. Svensson B, Hafstrom I, Forslind K, Albertsson K, Tarkowski A, Bokarewa M. Increased expression of proto-oncogene survivin predicts joint destruction and persistent disease activity in early rheumatoid arthritis. Annals of Medicine. 2010; 42(1):45-54

166. Syversen SW, Gaarder PI, Goll GL, Odegard S, Haavardsholm EA, Mowinckel P et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. Annals of the Rheumatic Diseases. 2008; 67(2):212-217

167. Syversen SW, Goll GL, van der Heijde D, Landewe R, Gaarder PI, Odegard S et al. Cartilage and bone biomarkers in rheumatoid arthritis: prediction of 10-year radiographic progression. Journal of Rheumatology. 2009; 36(2):266-272

168. Syversen SW, Goll GL, van der Heijde D, Landewe R, Lie BA, Odegard S et al. Prediction of radiographic progression in rheumatoid arthritis and the role of antibodies against mutated citrullinated vimentin: results from a 10-year prospective study. Annals of the Rheumatic Diseases. 2010; 69(2):345-351

169. Syversen SW, Haavardsholm EA, Boyesen P, Goll GL, Okkenhaug C, Gaarder PI et al. Biomarkers in early rheumatoid arthritis: longitudinal associations with inflammation and joint destruction measured by magnetic resonance imaging and conventional radiographs. Annals of the Rheumatic Diseases. 2010; 69(5):845-850

170. Tamai M, Arima K, Nakashima Y, Kita J, Umeda M, Fukui S et al. Baseline MRI bone erosion predicts the subsequent radiographic progression in early rheumatoid arthritis patients who achieved sustained good clinical response. Modern Rheumatology. 2017:1-6

171. Tanaka N, Sakahashi H, Ishii S, Sato E, Hirose K, Ishima T. Synovial membrane enhancement and bone erosion by magnetic resonance imaging for prediction of radiologic progression in patients with early rheumatoid arthritis. Rheumatology International. 2005; 25(2):103-107

172. Tobon G, Saraux A, Lukas C, Gandjbakhch F, Gottenberg JE, Mariette X et al. First-year radiographic progression as a predictor of further progression in early arthritis: results of a large national French cohort. Arthritis Care & Research. 2013; 65(12):1907-1915

173. Tugnet N, Pearce F, Tosounidou S, Obrenovic K, Erb N, Packham J et al. To what extent is NICE guidance on the management of rheumatoid arthritis in adults being implemented in clinical practice? A regional survey. Clinical Medicine. 2013; 13(1):42-46

174. Twigg S, Hensor EMA, Emery P, Tennant A, Morgan AW, Yorkshire Early Arthritis Register Consortium. Patient-reported outcomes as predictors of change in disease activity and disability in early rheumatoid arthritis: results from the Yorkshire Early Arthritis Register. Journal of Rheumatology. 2017; 44(9):1331-1340

175. Twigg S, Hensor EMA, Freeston J, Tan AL, Emery P, Tennant A et al. Fatigue, older age, higher body mass index and female gender predict worse disability in early

rheumatoid arthritis despite treatment to target: A comparison of two observational cohort studies from the United Kingdom. Arthritis Care & Research. 2017; Epublication

176. Valenzuela-Castano A, Garcia-Lopez A, Perez-Vilches D, Rodriguez-Perez R, Gonzalez-Escribano MF, Nunez-Roldan A. The predictive value of the HLA shared epitope for severity of radiological joint damage in patients with rheumatoid arthritis. A 10 year observational prospective study. Journal of Rheumatology. 2000; 27(3):571-574

177. van den Broek M, Dirven L, de Vries-Bouwstra JK, Dehpoor AJ, Goekoop-Ruiterman YP, Gerards AH et al. Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up. Annals of the Rheumatic Diseases. 2012; 71(9):1530-1533

178. van den Broek M, Dirven L, Kroon HM, Kloppenburg M, Ronday HK, Peeters AJ et al. Early local swelling and tenderness are associated with large-joint damage after 8 years of treatment to target in patients with recent-onset rheumatoid arthritis. Journal of Rheumatology. 2013; 40(5):624-629

179. van der Heide A, Jacobs JW, Haanen HC, Bijlsma JW. Is it possible to predict the first year extent of pain and disability for patients with rheumatoid arthritis? Journal of Rheumatology. 1995; 22(8):1466-1470

180. van der Heijde DM, van Riel PL, van Leeuwen MA, van't Hof MA, van Rijswijk MH, van de Putte LB. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. British Journal of Rheumatology. 1992; 31(8):519-525

181. van der Kooi E, Klarenbeek NB, Guler-Yuksel M, Kerstens PJ, van der Lubbe PA, Westedt ML et al. A decrease in disease activity score (DAS) level is associated with a decrease in health assessment questionnaire (HAQ) score, independent of follow-up duration, during 5 years of tightly controlled treatment: results from the BeSt study. Annals of the Rheumatic Diseases. 2011; 70(1):168-171

182. van der Linden MP, Feitsma AL, le Cessie S, Kern M, Olsson LM, Raychaudhuri S et al. Association of a single-nucleotide polymorphism in CD40 with the rate of joint destruction in rheumatoid arthritis. Arthritis & Rheumatism. 2009; 60(8):2242-2247

183. van der Linden MP, van der Woude D, Ioan-Facsinay A, Levarht EW, Stoeken-Rijsbergen G, Huizinga TW et al. Value of anti-modified citrullinated vimentin and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. Arthritis & Rheumatism. 2009; 60(8):2232-2241

184. van der Woude D, Syversen SW, van der Voort EI, Verpoort KN, Goll GL, van der Linden MP et al. The ACPA isotype profile reflects long-term radiographic progression in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010; 69(6):1110-1116

185. van Leeuwen MA, van Rijswijk MH, van der Heijde DM, Te Meerman GJ, van Riel PL, Houtman PM et al. The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. British Journal of Rheumatology. 1993; 32 (Suppl 3):9-13

186. van Leeuwen MA, Westra J, van Riel PL, Limburg PC, van Rijswijk MH. IgM, IgA, and IgG rheumatoid factors in early rheumatoid arthritis predictive of radiological progression? Scandinavian Journal of Rheumatology. 1995; 24(3):146-153

187. van Nies JA, van Steenbergen HW, Krabben A, Stomp W, Huizinga TW, Reijnierse M et al. Evaluating processes underlying the predictive value of baseline erosions for future radiological damage in early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2015; 74(5):883-889

188. van Steenbergen HW, Raychaudhuri S, Rodriguez-Rodriguez L, Rantapaa-Dahlqvist S, Berglin E, Toes RE et al. Association of valine and leucine at HLA-DRB1 position 11 with radiographic progression in rheumatoid arthritis, independent of the shared epitope alleles but not independent of anti-citrullinated protein antibodies. Arthritis & Rheumatology. 2015; 67(4):877-886

189. van Steenbergen HW, Tsonaka R, Huizinga TW, le Cessie S, van der Helm-van Mil AH. Predicting the severity of joint damage in rheumatoid arthritis; the contribution of genetic factors. Annals of the Rheumatic Diseases. 2015; 74(5):876-882

190. van Tuyl LH, Voskuyl AE, Boers M, Geusens P, Landewe RB, Dijkmans BA et al. Baseline RANKL:OPG ratio and markers of bone and cartilage degradation predict annual radiological progression over 11 years in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010; 69(9):1623-1628

191. van Zeben D, Hazes JM, Zwinderman AH, Vandenbroucke JP, Breedveld FC. Factors predicting outcome of rheumatoid arthritis: results of a followup study. Journal of Rheumatology. 1993; 20(8):1288-1296

192. Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen JS. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology. 2009; 48(9):1114-1121

193. Vencovsky J, Machacek S, Sedova L, Kafkova J, Gatterova J, Pesakova V et al. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2003; 62(5):427-430

194. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Annals of the Rheumatic Diseases. 2010; 69(7):1333-1337

195. Vittecoq O, Pouplin S, Krzanowska K, Jouen-Beades F, Menard JF, Gayet A et al. Rheumatoid factor is the strongest predictor of radiological progression of rheumatoid arthritis in a three-year prospective study in community-recruited patients. Rheumatology. 2003; 42(8):939-946

196. Wagner E, Ammer K, Kolarz G, Krajnc I, Palkonyai E, Scherak O et al. Predicting factors for severity of rheumatoid arthritis: a prospective multicenter cohort study of 172 patients over 3 years. Rheumatology International. 2007; 27(11):1041-1048

197. Wechalekar MD, Lester S, Hill CL, Lee A, Rischmueller M, Smith MD et al. Active foot synovitis in patients with rheumatoid arthritis: unstable remission status, radiographic progression, and worse functional outcomes in patients with foot synovitis in apparent remission. Arthritis Care & Research. 2016; 68(11):1616-1623

198. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis & Rheumatism. 2001; 44(9):2009-2017

199. Wevers-de Boer KV, Heimans L, Visser K, Kalvesten J, Goekoop RJ, van Oosterhout M et al. Four-month metacarpal bone mineral density loss predicts radiological joint damage progression after 1 year in patients with early rheumatoid arthritis:

exploratory analyses from the IMPROVED study. Annals of the Rheumatic Diseases. 2015; 74(2):341-346

200. Wiles N, Dunn G, Barrett E, Silman A, Symmons D. Associations between demographic and disease-related variables and disability over the first five years of inflammatory polyarthritis: a longitudinal analysis using generalized estimating equations. Journal of Clinical Epidemiology. 2000; 53(10):988-996

201. Winfield J, Young A, Williams P, Corbett M. Prospective study of the radiological changes in hands, feet, and cervical spine in adult rheumatoid disease. Annals of the Rheumatic Diseases. 1983; 42(6):613-618

202. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis & Rheumatism. 1998; 41(9):1571-1582

203. Yamazaki H, Hirano F, Takeuchi T, Amano K, Kikuchi J, Kihara M et al. Simplified Disease Activity Index remission at month 6 is an independent predictor of functional and structural remissions at month 12 during abatacept treatment in patients with rheumatoid arthritis: A multi-center, prospective cohort study in Japan. Modern Rheumatology. 2016; 27(5):787-794

204. Young-Min S, Cawston T, Marshall N, Coady D, Christgau S, Saxne T et al. Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers. Arthritis & Rheumatism. 2007; 56(10):3236-3247

205. Young A, Corbett M, Winfield J, Jaqueremada D, Williams P, Papasavvas G et al. A prognostic index for erosive changes in the hands, feet, and cervical spines in early rheumatoid arthritis. British Journal of Rheumatology. 1988; 27(2):94-101

206. Zavada J, Hanova P, Hurnakova J, Szczukova L, Uher M, Forejtova S et al. The relationship between synovitis quantified by an ultrasound 7-joint inflammation score and physical disability in rheumatoid arthritis - a cohort study. Arthritis Research & Therapy. 2017; 19:5

1 Appendices

2 Appendix A: Review protocols

3 **Table 9: Review protocol: Poor function**

ID	Field	Content
I	Review question	In adults with rheumatoid arthritis, which risk factors are associated with poorer long-term function as measured by the Health Assessment Questionnaire?
II	Type of review question	Prognostic review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	To evaluate the association between HAQ scores at first presentation, elevated CRP, elevated ESR, presence of RF, presence of CCP or X-ray damage at first presentation, and poorer long-term function as measured by the Health Assessment Questionnaire, in adults with rheumatoid arthritis.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis according to validated classification criteria, who are not receiving DMARD treatment at the point of measurement of prognostic factors (prior DMARD use with wash-out is acceptable)
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• HAQ scores at first presentation • Elevated levels of CRP • Elevated levels of ESR • Presence or absence of RF • Presence or absence of CCP • Presence or absence of X-ray erosion at first presentation • Combinations of these factors (algorithm) Presence of any laboratory test factor will be determined in accordance with the laboratories methods and thresholds. Presence needs to be in absence of any other known cause (for example, co-existent infection or malignancy for inflammatory markers). Studies will still be included where erosions at first presentation are measured using a different imaging modality (for example, MRI) or are reported as continuous data using a validated scale (for example, Sharp/Larsen/van der Heijde).
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Not applicable.
VII	Outcomes and prioritisation	Health assessment questionnaire (HAQ) (continuous) at 12 months or more Studies will still be included where the outcome is reported as dichotomous data (for example, number of patients above/below a HAQ score threshold).

ID	Field	Content
		If a study reports outcomes at multiple time points, the closest time point to 12 months (that is at least 12 months) will be reported.
VIII	Eligibility criteria – study design	Prospective cohort studies. For a study to be considered "prospective", the data collection must be prospective from the point of recruitment of patients into the cohort/trial. Retrospective cohort studies will be included only if no prospective cohort studies are identified.
IX	Other inclusion exclusion criteria	Studies will only be included if all the key confounders have been accounted for in a multivariate analysis.
X	Proposed sensitivity / subgroup analysis, or meta-regression	None
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists will be double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus cannot be reached. For more information please see the separate Methods report for this guideline.
XII	Data management (software)	• Endnote will be used for bibliographies, citations, sifting and reference management
XIII	Information sources – databases and dates	Databases: The databases to be searched are Medline and Embase Date limits for search: None Language: English Health economics search databases: Medline, Embase, NHSEED and HTA Date limits for search: Medline and Embase from 2014 NHSEED and HTA from 2001 Language: English
XIV	Identify if an update	This review is not an update.
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details, please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).

ID	Field	Content
XX	Methods for assessing bias at outcome / study level	QUIPS tool was used for the evaluation of risk of bias for prognostic studies. The risk of bias across all available evidence was evaluated using a modified GRADE approach.
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual
XXVII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

1

2 **Table 10: Review protocol: Radiographic progression**

ID	Field	Content
I	Review question	In adults with rheumatoid arthritis, which risk factors are associated with worse radiological progression?
II	Type of review question	Prognostic review A review of health economic evidence related to the same review question

ID	Field	Content
		was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	To evaluate the association between elevated CRP, elevated ESR, presence of RF, presence of CCP or X-ray damage at first presentation, and radiological progression, in adults with rheumatoid arthritis.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis according to validated classification criteria, who are not receiving DMARD treatment at the point of measurement of prognostic factors (prior DMARD use with wash-out is acceptable)
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Elevated levels of CRP • Elevated levels of ESR • Presence or absence of RF • Presence or absence of CCP • Presence or absence of X-ray erosion at first presentation • Combinations of these factors (algorithm) Presence of any laboratory test factor will be determined in accordance with the laboratories methods and thresholds. Presence needs to be in absence of any other known cause (for example, co-existent infection or malignancy for inflammatory markers). Studies will still be included where erosions at first presentation are measured using a different imaging modality (for example, MRI) or are reported as continuous data using a validated scale (for example, Sharp, Larsen or van der Heijde).
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Not applicable
VII	Outcomes and prioritisation	Radiographic progression (continuous) at 12 months or more Studies will still be included where the outcome is reported as dichotomous data (for example, number of patients progressing at least two points versus those progressing less than two points). If a study reports outcomes at multiple time points, the closest time point to 12 months (that is at least 12 months) will be reported
VIII	Eligibility criteria – study design	Prospective cohort studies. For a study to be considered “prospective”, the data collection must be prospective from the point of recruitment of patients into the cohort/trial. Retrospective cohort studies will be included only if no prospective cohort studies are identified.
IX	Other inclusion exclusion criteria	Studies will only be included if all the key confounders have been accounted for in a multivariate analysis.
X	Proposed sensitivity / subgroup	None

ID	Field	Content
	analysis, or meta-regression	
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists will be double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus cannot be reached. For more information please see the separate Methods report for this guideline.
XII	Data management (software)	Endnote will be used for bibliographies, citations, sifting and reference management.
XIII	Information sources – databases and dates	Databases: The databases to be searched are Medline, Embase and the Cochrane Library. Date limits for search: None Language: English
XIV	Identify if an update	This review is not an update.
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details, please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	QUIPS tool will be used for the evaluation of risk of bias for prognostic studies. The risk of bias across all available evidence will be evaluated using a modified GRADE approach.
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective	For details, please see section 6.2 of Developing NICE guidelines: the manual.

ID	Field	Content
	reporting bias	
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual
XXVII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

1

2 **Table 11: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[126] Inclusion and exclusion criteria

Review question	All questions – health economic evidence
	If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies selectively. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017. https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using the following approach:

- Population AND Prognostic/risk factor terms AND Study filter

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (Ovid)	1946 – 09 October 2017	Exclusions Prognostic studies
Embase (Ovid)	1974 – 09 October 2017	Exclusions Prognostic studies

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp Animal Experimentation/
24.	exp Models, Animal/

25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	(haq or health assessment questionnaire).ti,ab.
30.	C-Reactive Protein/
31.	(crp or c-reactive protein*).ti,ab.
32.	(ccp or anti-ccp or cyclic citrullinated peptide*).ti,ab.
33.	((x-ray or xray) adj3 (erosion or damage*)).ti,ab.
34.	(bone* adj3 (erosion or erod*)).ti,ab.
35.	((radiograph* or radiolog*) adj2 (damage or progression)).ti,ab.
36.	or/29-35
37.	28 and 36
38.	predict.ti.
39.	prognosis/
40.	(validat* or rule*).ti,ab.
41.	(predict* and (outcome* or risk* or model*)).ti,ab.
42.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif*)).ti,ab.
43.	decision*.ti,ab. and Logistic models/
44.	(decision* and (model* or clinical*)).ti,ab.
45.	prognos*.ti,ab.
46.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
47.	ROC curve/
48.	or/38-47
49.	37 and 48

1 **Embase (Ovid) search terms**

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16

18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	*health assessment questionnaire/
28.	(haq or health assessment questionnaire).ti,ab.
29.	*C reactive protein/
30.	(crp or c-reactive protein*).ti,ab.
31.	*cyclic citrullinated peptide antibody/
32.	(ccp or anti-ccp or cyclic citrullinated peptide*).ti,ab.
33.	*bone erosion/
34.	((x-ray or xray) adj3 (erosion or damage*)).ti,ab.
35.	(bone* adj3 (erosion or erod*)).ti,ab.
36.	((radiograph* or radiolog*) adj2 (damage or progression)).ti,ab.
37.	or/27-36
38.	26 and 37
39.	predict.ti.
40.	prognosis/
41.	(validat* or rule*).ti,ab.
42.	(predict* and (outcome* or risk* or model*)).ti,ab.
43.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
44.	decision*.ti,ab. and Statistical model/
45.	(decision* and (model* or clinical*)).ti,ab.
46.	prognos*.ti,ab.
47.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
48.	Receiver operating characteristic/
49.	or/39-48
50.	38 and 49

B.21 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to rheumatoid arthritis population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used

Database	Dates searched	Search filter used
Medline	2014 – 06 October 2017	Exclusions Health economics studies
Embase	2014– 06 October 2017	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2001 – 06 October 2017 NHSEED - 2001 – 31 March 2015	None

1 **Medline (Ovid) search terms**

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/

35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/
38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

1 **Embase (Ovid) search terms**

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/

20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES
#2.	((rheumatoid adj2 (arthritis or arthrosis)))
#3.	((caplan* adj2 syndrome))
#4.	((felty* adj2 syndrome))

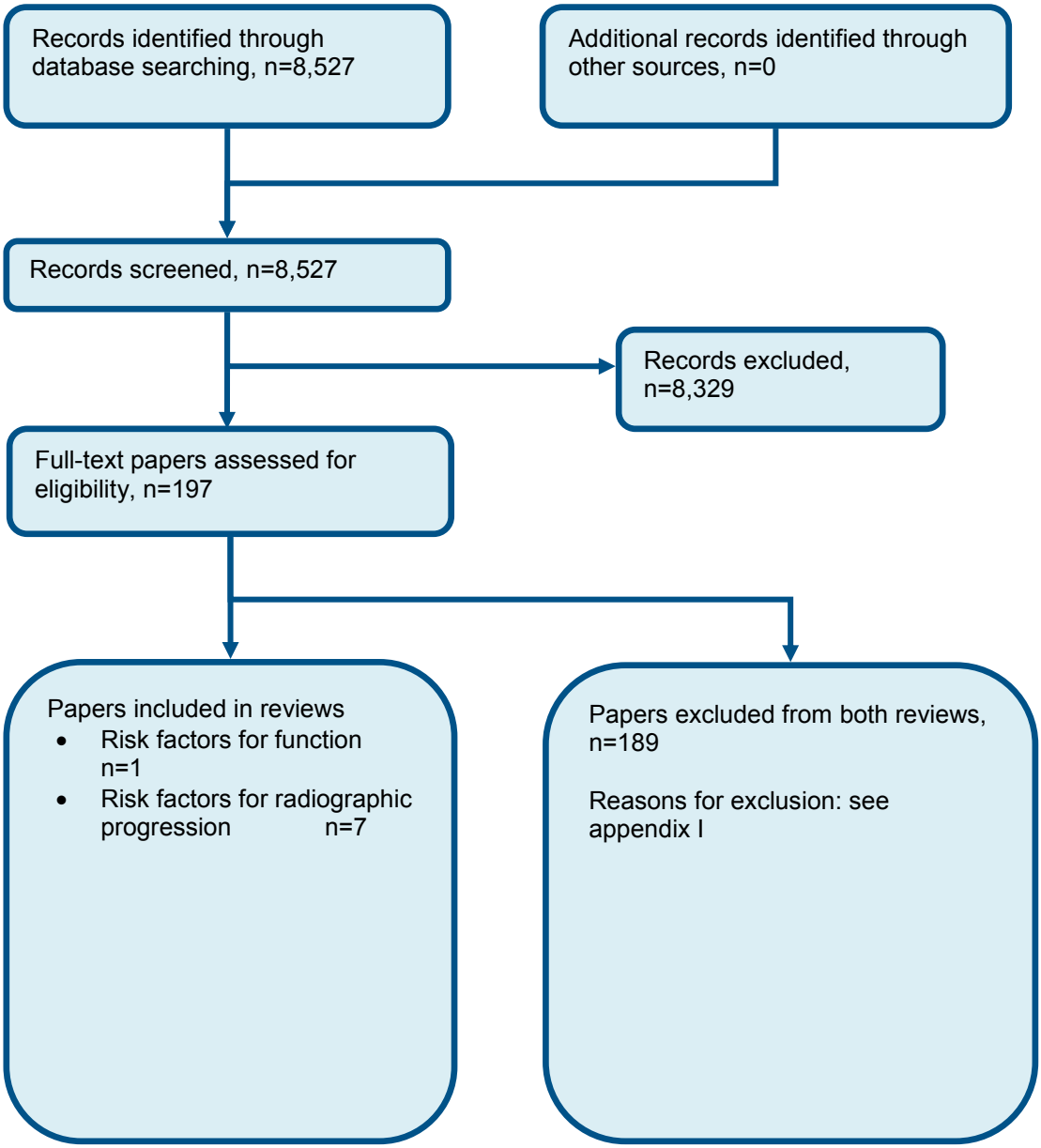
#5.	((rheumatoid adj2 factor))
#6.	(((inflammatory or idiopathic) adj2 arthritis))
#7.	("inflammatory polyarthritis")
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

1

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the reviews of prognostic factors in rheumatoid arthritis



Appendix D: Clinical evidence tables

Reference	Audo 2015[4, #2158]
Study type and analysis	Prospective cohort study (ESPOIR cohort) Stepwise multiple logistic regression
Number of participants and characteristics	n=399 Country: France Prognostic factors (baseline) of 399 patients: RF+, n (%): 203 (51) ACPA+, n (%): 180 (45) Total modified Sharp score, mean (SD): 3.8 (4.4) Inclusion criteria: Patients of the ESPOR cohort who fulfilled the ACR-EULAR 2010 criteria for the classification of Rheumatoid arthritis (RA). Exclusion criteria: Patients with a history of lymphoma and neoplasia (n=13) because of a known relation between cytokine tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and tumour genesis and those with the highest erosion scores (mSharp erosion score >90th percentile which corresponds to 4 points of the Sharp score; n=62). The authors state that 'radiographic erosion at baseline is a well-characterised factor of further radiographic progression, and the EULAR task force recommended prompt use of biological therapy in these rare cases.' Patients who had received biological therapy in the first 2 years (n=121) were also excluded as it strongly affects radiographic disease progression. Another n=46 not included for unexplained reasons (may be lost to follow up or missing data). Population characteristics (baseline) of 399 patients: Female, n (%): 323 (81) Age, mean (SD): 48.4 (11.9) DAS28 (ESR)-4v, mean (SD): 5.3 (1.2) HAQ score, mean (SD): 1.0 (0.7) Glucocorticoid use, n (%): 56 (14)

Reference	Audo 2015[4, #2158]
	Recruitment: The ESPOIR cohort is a prospective multicentre observational study of patients aged 18–70 who have early arthritis under the umbrella of the French Society for Rheumatology. 814 patients were recruited from December 2002 and March 2005 from 14 regional centres (16 university hospital rheumatology departments). Patients had a clinical diagnosis of rheumatoid arthritis as certain or probable or a clinical diagnosis of undifferentiated arthritis potentially becoming RA, at least 2 inflammatory joints since 6 weeks, arthritis starting since less than 6 months, never been prescribed DMARDs, never been prescribed corticoids except if less than 2 weeks at max mean dose of 20mg per day and at least 2 weeks before inclusion, or intra-articular (IA) injection less than 4 weeks before inclusion. Exclusion criteria were other inflammatory rheumatisms or connective tissue diseases clearly defined and early arthritis with no potential chance to become RA. DMARD use after inclusion: treatment by rheumatologists followed the standard of care (specific treatments not reported but use of conventional disease-modifying anti-rheumatic drugs (cDMARDs) appear to be approximately 79–85% of population).
Prognostic variable(s)	ACPA+, logCRP level, ESR, RF+, radiographic progression (total modified Sharp score)
Confounders	Univariate analysis considered above variables plus: age, sex, BMI, DAS28(ESR)-4v, glucocorticoid use, cDMARD use, logOPG/TRAIL ratio Q<25 (%), logGPG/TRAIL ratio Q25-75 (%), logOPG/TRAIL ratio Q >75 (%)
Outcomes and effect sizes	Outcome: rapid erosion progression (change in Sharp erosion score >5) at 2 years Variables entered into model: age, RF+, ACPA, logCRP level, ESR, logGPG/TRAIL ratio Q25-75 (%) Rapid radiographic progression was defined by at least a 5 point per year increase in total mSharp score, which corresponds to a 10-point increase at 2 years. Because erosion and joint-space narrowing are almost similar to total Sharp score, the authors defined rapid progression of erosion, as at least a 5-point increase in erosion score or joint-space narrowing score at 2 years. Univariate analysis was reported for all 3 outcomes (rapid radiological progression, rapid erosion progression and rapid joint-space narrowing progression), but the outcomes of multivariate logistic regression were only fully reported for the outcome of rapid erosion progression. All covariates associated at the 20% level (p<0.20) on univariate analysis were included in the multivariate logistic regression model as potential confounding confounders and selected by stepwise multiple regression. Results: Final model included ACAP+, logCRP, age and logOPG/TRAIL ratio (per category increase). ACPA+ (versus negativity): OR 3.95 (95% CI 1.26–12.44) logCRP (per log unit): OR 2.01 (95% CI 0.83- 4.87) Other prognostic factors (ESR, RF+, total modified Sharp score) were not independently associated with the outcome of rapid erosion progression (p=0.55, p=0.21, p=0.77 respectively).

Reference	Audo 2015[4, #2158]
	Authors notes regarding rapid radiographic progression (total mSharp score) outcome data: "On multivariate logistic regression, age, ACPA positivity and CRP level, but not ESR, RF positivity and logOPG/TAIL ratio, were associated with rapid radiographic progression (total mSharp score)." "Total mSharp score was strongly associated with radiographic progression in all ESPOIR RA patients (p<0.001) [rather than just those included in the study]. Thus, excluding patients with the highest erosion scores at baseline, as was done in this study, removed any of the total mSharp score predictive value for rapid radiographic progression."
Comments	Very high risk of bias (study participation – exclusion of those with highest sharp scores; study attrition – missing data not reported/explained; outcome measurement – unclear if assessors blinded or whether any adjustment for inter-rater measurement errors; statistical analysis – selective outcome reporting.)

1

Reference	Courvoisier 2008[32]
Study type and analysis	Prospective cohort study Stepwise multiple logistic regression
Number of participants and characteristics	n=191 (112 analysed) Country: France Prognostic factors (baseline) of 112 patients: IgA or IgM RF+, n (%): 81 (78.6) Anti-CCP+, n (%): 51 (57.9) ESR in mm, mean (SD): 37.6 (26.7) CRP in mg/l, mean (SD): 29.1 (39.8) Sharp/van der Heijde score, mean (SD): 5.8 (9.0) Inclusion criteria: Patients fulfilling the ACR criteria for the classification of RA for ≤ 1 year at the start of the study. Exclusion criteria: Patients previously treated with DMARDs. Population characteristics (baseline) of 112 patients: Female, n (%): 90 (80.3)

Reference	Courvoisier 2008[32]
	Age, mean (SD): 50.4 (12.6) Disease duration, months, mean (SD): 3.9 (2.8) DAS, mean (SD): 4.0 (0.7) HAQ score, mean (SD): 1.29 (0.71) Recruitment: All consecutive outpatients matching the inclusion criteria were referred to the study by primary care physicians from 4 French centres, Montpellier, Paris-Cochin, Toulouse and Tours between March 1993 and October 1994. After inclusion, all patients were treated with DMARDs (methotrexate, sulfasalazine or both) that could be modified during the study according to efficacy and side effects. DMARD use during the 10 years of follow-up: methotrexate: 76.7%, sulfasalazine: 51.7%, methotrexate + sulfasalazine: 29.4%, gold salts: 29.4%, hydroxychloroquine: 21.4%, leflunomide: 21.4%, D-penicillamine: 1.7%, ciclosporin: 3.5%, etanercept: 10.7%, infliximab: 8.0%, adalimumab: 3.5%, anakinra: 0.8%, abatacept: 0.8%. The authors stated that they could not acquire precise data on the use of oral glucocorticoids over the 10-year period, as most patients received such drugs at various times and dosages. Nevertheless, 33% of the patients who were evaluated after 3 years and 34.6% evaluated after 5 years had received a low dose of prednisone (5 to 15 mg per day).
Prognostic variable(s)	ACPA, anti-CCP antibodies, CRP, ESR, IgA and IgM RF+, radiographic progression (total Sharp score, erosion score, joint narrowing score)
Confounders	Univariate analysis considered above variables plus: serum level of MMP3, level of IgA and IgM RF, swollen joint count, morning stiffness, HLA-DRB1*01, tender joint count, CRP, DAS, anti-keratin antibodies, age, sex, pain on VAS, YKL 40, anti-perinuclear antibodies, anti-nuclear antibodies, extra-articular signs, Ritchie score, anti-HSP90 antibodies, HAQ score
Outcomes and effect sizes	Outcome: 'above median' radiographic Sharp score at 10 years Variables entered into model: ESR; positivity for and level of IgA RF; positivity for anti-perinuclear, anti-CCP and ACPA; serum level of MMP3; and radiographic scores (erosion score, joint narrowing score and total Sharp score) Continuous outcome variables were transformed into dichotomous variables with the median value used as cut-off: for example, higher or lower than the median value for the total Sharp score at 10 years. OMERACT was used to determine the minimum clinically important difference (MCID) for the modified Sharp score to be 5 points. A stepwise multiple logistic regression model was used to determine relevant independent prognostic variables. The prognostic variables included in the model were selected from results of the univariate analysis (entry level was set at p=0.10). The overall significance level was set at 0.05 for the whole study. Results:

Reference	Courvoisier 2008[32]
	Erosion score: OR 5.64 (95% CI 1.78–17.86) Other prognostic factors (CRP, ESR, RF, CCP, total Sharp score) were not independently associated with the outcome.
Comments	Very high risk of bias (outcome measurement – arbitrary median value of Sharp score was used to categorise outcome into lower and higher radiographic progression; statistical analysis – authors report univariate analysis of radiographic progression but then do not report MVA of it)

1

Reference	Forslind 2012[57]
Study type and analysis	Prospective cohort study: BARFOT Multiple logistic regression
Number of participants and characteristics	n=839 (379 included in analysis) Country: Sweden Prognostic factors (baseline). Percentages reported in paper appear to be incorrect. New calculations of these used. RF+ n (%): 221 (58%) Anti-CCP +: 210 (55%) ESR, mean (SD): 38 (26) CRP, mg/L, mean (SD): 37 (38) Sharp score, mean (SD): 4 (8.2) Erosion score, mean (SD): 1.7 (3.8) Inclusion criteria: People aged 18 to 80 with resent onset RA (<1 year) fulfilling the 1987 ACR criteria. Exclusion criteria: None detailed Population characteristics: Female: 241 (64%) Age, mean (SD): 57 (15) Disease duration, months, mean (SD): 6.3 (3.2) DAS28, mean (SD): 5.07 (1.2) People treated according to clinical judgement of their rheumatologist except 166 people who were in a low dose glucocorticoid study.

Reference	Forslind 2012[57]
	DMARD prescribed at baseline: none: 77 (20%), methotrexate: 155 (41%), sulfasalazine: 102 (27%), other DMARD: 44 (12%), combination: 1 (0%), biologics: 0 (0%) Recruitment: people consecutively enrolled in study at 6 centres in Sweden between 1993 and 1999.
Prognostic variable(s)	RF+, anti-CCP+, ESR (continuous), CRP (continuous), Sharp score (continuous), presence of erosions
Confounders	Univariate analysis considered demographic and clinical data collected at baseline and at 1 year. The following variables (at baseline unless otherwise stated) were univariately associated with radiographic progression at 2, 5 and 8 years: ChDXR at 1 year, HBLsdc, HBLtertiles, ChSHS at 1 year, presence of erosions, anti-CCP and number of swollen joints at 1 year. The following variables were univariately associated with radiographic progression at 5 years: DAS28 at 1 year, ESR, ESR at 1 year, HAQ at 1 year, CRP a 1 year. The following variables were univariately associated with radiographic progression at 8 years: tender joints, tender joints at 1 year. Age, disease duration, gender, smoking, baseline DMARD and glucocorticoid treatment, baseline DXR-BMD treatment were not associated with radiographic progression at any time point.
Outcomes and effect sizes	Outcome: Radiographic progression: SvdH score change of >5.8 at 2 years. 145 (38%) progressed in 2 years Variables entered into model: change in DXR at 1 year, change in SvdH score at 1 year, erosions at baseline, anti-CCP, number of swollen joints at 1 year, DAS28 at 1 year, general health at 1 year, ESR at baseline, ESR at 1 year, HAQ at 1 year, CRP at 1 year Variables significantly associated with radiographic progression in the univariate analysis were out into multiple regression analysis. Results: Final model, with X-ray scores, included: change in DXR at 1 year, change in SvdH score at 1 year, erosions at baseline, anti-CCP, number of swollen joints at 1 year, DAS28 at 1 year, general health at 1 year, ESR at baseline, ESR at 1 year, HAQ at 1 year, CRP at 1 year Erosions at baseline: OR 0.666 (95% CI 0.262–1.691) Anti-CCP+: OR 3.475 (95% CI 1.332–9.066) ESR at baseline: OR 0.999 (95% CI 0.979–1.018) Note that the final model included multiple variables measured at 1 year. The inclusion of factors at 1 year may have an effect on the odds ratios of the baseline prognostic factors in which this review is interested. CRP at baseline was not independently associated with the outcome.
Comments	High risk of bias (study attrition – only 45% had radiographs suitable for inclusion at baseline and 1 year) Serious indirectness due to due to final model including multiple variables measured at 1 year.

1

Reference	Graell 2009[69]
Study type and analysis	Prospective cohort study Binary multivariate logistic regression
Number of participants and characteristics	n=115 (105 analysed) Country: Spain Prognostic factors (baseline) of 105 patients: RF+, n (%): 77 (73%) Anti-CCP +, n (%): 74 (70%) ESR, mm/h, mean (SD): 39.5 (24.5) CRP, mg/dL, mean (SD): 2.8 (2.9) Larsen score, mean (SD): 1.2 (2.7) MHAQ, mean (SD): 0.97 (0.56) Inclusion criteria: Patients fulfilling the ACR criteria for the classification of RA, with symptoms for < 24 months Exclusion criteria: Patients previously treated with DMARDs, prednisone, or equivalent at a dose > 10mg per day Population characteristics (baseline) of 105 patients: Female, n (%): 85 (81%) Age, mean (SD): 55 (14.9) Disease duration, months, mean (SD): 10 (6.7) DAS28, mean (SD): 5.66 (0.91) DMARD use at follow up (2 years): Gold salts monotherapy: 28.6%, gold salts and methotrexate: 10.5%, methotrexate monotherapy: 21.9%, methotrexate combined 12.4%, other DMARDs 12.4%, no DMARDs: 14.2%, methyl-prednisolone: 62.5%. Recruitment: Patients meeting the inclusion criteria were enrolled in the study. All were outpatients attending the rheumatology units of the Hospital Clinic of Barcelona or the Hospital Parc Tauli of Sabadell between 1998 and 2003.
Prognostic variable(s)	RF, anti-CCP, ESR, CRP, Larsen score, mHAQ continuous score, mHAQ > 0.5

Reference	Graell 2009[69]
Confounders	Univariate analysis considered above variables plus sex, age, disease duration, marital status, hand workers, university studies, active work patients, HLS-DRB1-04, shared epitope, Haemoglobin, 28 tender joint count, 28 swollen joint count, patient's global assessment, physician global assessment, VAS pain, DAS28 (continuous), DAS28 > 5.1.
Outcomes and effect sizes	Outcome: Disability (MHAQ>0) at 2 years (77/105 patients experienced outcome) Variables entered into model: Specific variables not stated. Variables showing significance or trends in univariate analysis between baseline and 6 months were considered effect modifying. Clinically relevant interactions were included and the forward stepwise conditional technique was used to obtain the final model. Results: Final model included age, RF+ status, and baseline MHAQ (>0.5) RF+: OR 3.772 (95% CI 1.204 – 11.813) MHAQ > 0.5: OR 4.023 (95% CI 1.373 – 11.783) Other prognostic factors (ESR, CRP, Larsen score, MHAQ continuous) were not independently associated with the outcome
Comments	Very high risk of bias (outcome cut-off, statistical analysis – methods unclear)

1

Reference	Güler-Yüksel 2010[72]
Study type and analysis	Analysis of population in a randomised controlled trail (RCT) (BeST) Multiple logistic regression
Number of participants and characteristics	n=272 (256 analysed) Country: the Netherlands Prognostic factors (baseline) of 256 patients: RF+, n (%): 159 (62%) ACPA +, n (%): 133 (62%; data on 247 patients, not all at baseline) ESR, mm/h, median (IQR): 37 (19-54) CRP, mg/dL, median (IQR): 20 (9-58) Total SHS score, mean (SD): 5.9 (8.2; data on 248 patients) Presence erosive damage ≥1 unit, n (%): 174 (70%; data on 248 patients) Inclusion criteria: Patients enrolled in the BeST trial (see recruitment below).

Reference	Güler-Yüksel 2010[72]
	Exclusion criteria: Patients from the BeST trial with digital radiographs (236/508 excluded for this reason). 16 eligible patients not included in analysis due to inability to analysed radiographs by DXR. Population characteristics (baseline) of 256 patients: Female, n (%): 166 (65%) Age, mean (SD): 54 (14) Disease duration, weeks, median (IQR): 2 (1-5) Symptom duration, weeks, median (IQR): 24 (14-53) DAS, mean (SD): 4.4 (0.9) HAQ, mean (SD): 1.4 (0.6) DMARD use over study duration (% randomised to each arm of trial): 25% sequential monotherapy, 23% step-up therapy, 27% initial combi therapy with prednisone, 26% initial combi therapy with infliximab. Recruitment: Conducted in 18 peripheral and 2 university hospitals in the western part of the Netherlands. Patients aged ≥ 18 years, who met the definition of RA as defined by the ACR 1987 revised criteria, with symptom duration of less than 2 years and active disease with 6 or more of 66 swollen joints and 6 or more of 68 tender joints and either an ESR of 28 mm per hour or more or a VAS global health of 20 mm or more, and who were DMARD naïve, were included in the BeST trial from April 2000 to August 2002.
Prognostic variable(s)	RF+, ACPA+, ESR ≥ 30 mm/h, CRP ≥ 10 mg/L, SHS ≥ 1 unit
Confounders	Univariate analysis considered above variables plus: baseline variables: gender, age ≥ 50 years, postmenopausal status, BMI ≥ 25 kg/m2, symptom duration ≥ 6 months, number of swollen joints ≥ 10, Richie articular index ≥ 10, HAQ ≥ 1.057 units; first year follow-up variables: high AUC number of swollen joints, high AUC Ritchie articular index, high AUC ESR, high AUC CRP, delta HAQ ≤ -0.22 units, progressive SHS ≥ 5 units, hand BMD loss > 0.003 g/cm2 (first follow-up variables were adjusted for treatment group and the use of intraarticular glucocorticoids injections and antiresorptive therapy).
Outcomes and effect sizes	Outcome: Progressive total joint damage (≥ 5 units) between years 1-4 (77/256 patients experienced outcome) Variables entered into model: baseline: ACPA+, RF+, SHS ≥ 1 unit; first year follow-up: high AUC ESR, high AUC CRP, hand BMD loss > 0.003 g/cm2. Both significant (P < 0.05) and borderline significant (0.05 < P < 0.10) predictors derived from the univariate analyses (except for first year progressive SHS ≥ 5 units) were entered in multiple multivariate logistic regression analyses to determine the independent predictors of subsequent progressive joint disease.

Reference	Güler-Yüksel 2010[72]
	Results: Final model included all variables entered into model (see above). ACPA+: OR 3.95 (95% CI 1.17 – 15.0) RF+: OR 1.10 (0.38 – 2.98) SHS ≥ 1 unit (baseline): OR 5.87 (1.23 – 28.1) Other prognostic factors (ESR ≥ 30 mm/h, CRP ≥ 10 mg/L) were not independently associated with the outcome. Note that the final model included multiple variables measured at 1 year. The inclusion of factors at 1 year may have an effect on the odds ratios of the baseline prognostic factors in which this review is interested.
Comments	Low risk of bias. Serious indirectness (inclusion of variables measured at 1 year in final model).

1

Reference	Hetland 2009[78]
Study type and analysis	Multicentre RCT: CIMESTRA Multiple linear regression
Number of participants and characteristics	n=160 (130 included in MRI sub-study analysed here) Country: Denmark Prognostic factors (baseline) of 130 people included in analysis IgM RF+ n (%): 67 (52%) Anti-CCP +: 61 (47%) ESR, mean (IQR): unclear CRP, mg/L, mean (IQR): Unclear Erosive disease: 62 (48%) Total Sharp score, mean (SD): 5.2 (6.8) Inclusion criteria: Consecutive patients with early active RA according to the 1987 ACR criteria. DMARD naive and active disease for <6 months. At least 2 swollen joints and aged 18–75 years old. Exclusion criteria: None detailed. Reasons for exclusion from MRI sub-study: contraindications for MRI (n=3), disease activity that did

Reference	Hetland 2009[78]
	not allow for MRI (n=8), anxiety/claustrophobia (n=5), participant refusal (n=7), unknown (n=1) Population characteristics (n=130): Female: 85 (65%) Age, mean: 53.2 Disease duration, months, mean (IQR): 3.3 (2.6-4.9) DAS28, mean (IQR): 5.6 (4.7-6.1) Participants were treated aggressively to achieve tight disease control with conventional DMARDs. In the first year, methotrexate and either placebo or ciclosporin. In the second year, the placebo or ciclosporin was tapered to zero and hydroxychloroquine utilised. Recruitment: RCT recruiting consecutive patients from 5 rheumatology centres in Denmark from October 1999 to October 2002.
Prognostic variable(s)	RF+, anti-CCP+, ESR (continuous), CRP (continuous), Total Sharp Score (continuous)
Confounders	Univariate analysis considered above variables and gender, age, DAS28, disease duration, SJC, TJC, HAQ, patient global disease activity, doctor global disease activity, patient pain, smoker, HLA-DRB1-SE, IgA RF, school, MRI erosion score, MRI synovitis score, MRI bone oedema.
Outcomes and effect sizes	Outcome: Radiographic progression: change in TSS at 2 years. 39 (30%) progressed in 2 years Variables entered into model: gender, age, DAS28, ever smoker, anti-CCP, ever smoker and anti-CCP, HLA-DRB1-SE, MRI erosion score, MRI synovitis score, MRI bone oedema score, TSS Results: Initial model extracted: gender, age, DAS28, ever smoker, anti-CCP, ever smoker and anti-CCP, HLA-DRB1-SE, MRI erosion score, MRI synovitis score, MRI bone oedema score, TSS Total Sharp score: coefficient: 0.09 (-0.05 - 0.22) Anti-CCP+: coefficient: 2.94 (-0.1 - 5.98) CRP, ESR, RF+ were not associated with the outcome in the univariate analysis.
Comments	Low risk of bias

1

Reference	Quintana-Duque 2016[144]
Study type and	Prospective cohort study

Reference	Quintana-Duque 2016[144]
analysis	Stepwise multiple logistic regression
Number of participants and characteristics	n=159 (129 included in analysis due to withdrawal from study) Country: Columbia Prognostic factors (baseline): RF+: n (%) 91 (70.5%) Anti-CCP +: 90 (69.7%) ESR, mm/h, mean (SD): 29.7 (14.5) CRP, mg/dL, mean (SD): 1.95 (2.4) Presence of erosions: 42 (32.6%) Inclusion criteria: People with early onset rheumatoid arthritis (EORA). Disease duration <12 months. Fulfilling 1987 and 2010 ACR criteria for the classification of RA. Exclusion criteria: current or previous use of DMARDs or oral glucocorticoids, presence of other inflammatory arthropathies, serious medical disorders, women of childbearing age without adequate contraceptive protection. Population characteristics: Female: 101 (78.2%) Age, mean (SD): 46.6 (14.6) Disease duration, months, mean (SD): 4.29 (3) DAS28, mean (SD): 6.73 (0.9) DMARD use at follow up (3 years): methotrexate monotherapy: 20 (16%), methotrexate and chloroquine/hydroxychloroquine: 80 (62%), methotrexate and sulfasalazine: 29 22%). Recruitment: Attending rheumatology unit of the Universidad Nacional de Colombia or the Clinica de Artritis y Rehabilitacion (CAYRE).
Prognostic variable(s)	ESR (continuous), CRP (continuous), CCP+, RF+, presence of erosions, SvdH score (continuous)
Confounders	Univariate analysis considered above variables plus: age, gender, education, smoking history, family history, symptom duration, time between onset and diagnosis, joint with start of symptom, swollen joint count, tender joint count, morning stiffness, fatigue, pain, patient global disease activity assessment, physician global disease activity assessment, HAQ, DAS28, SDAI, CDAI, various genetic

Reference	Quintana-Duque 2016[144]
	genotypes, Anti-SSA/Ro autoantibodies, Antinuclear Antibodies (ANAs), therapy utilised.
Outcomes and effect sizes	Outcome: Radiographic progression at 3 years, defined as an increase in total SvdH of 3 units. 81 (63%) experienced this outcome. Variables entered into model: Variables selected using univariate analysis (p<0.1). Baseline parameters identified by the multiple logistic regression model that were independently predictive of radiographic progression at 3 years. Results: Final model included ESR, presence of erosion, SvdH. All at baseline. ESR: Exp (B) / OR 1.043 (95% CI 1.01 – 1.07) Presence of erosion: Exp (B) / OR 3.12 (95% CI 1.21 – 8.03) SvdH: Exp (B) / OR 1.06 (95% CI 1.005 – 1.13) Other prognostic factors (CRP, CCP, RF) were not independently associated with the outcome.
Comments	High risk of bias (study participation – sampling time frame and recruitment not adequately described)

1

Reference	Sanmarti 2007[157]
Study type and analysis	Prospective cohort study Stepwise multivariate logistic regression
Number of participants and characteristics	n=115 (105 analysed) Country: Spain Prognostic factors (baseline) of 105 patients: RF+, n (%): 78 (74.3) Anti-CCP2 +, n (%): 74 (70.4) ESR, mm/h, mean (SD): 39.6 (24.5) CRP, mg/dL, mean (SD): 2.8 (2.9) Larsen score, mean (SD): 1.2 (2.7) mHAQ, mean (SD): 1.0 (0.6) Inclusion criteria: Patients fulfilling the ACR criteria for the classification of RA, with symptoms for < 24 months.

Reference	Sanmarti 2007[157]
	Exclusion criteria: Patients previously treated with DMARDs or prednisone or equivalent at a dose > 10 mg per day. Population characteristics (baseline) of 105 patients: Female, n (%): 85 (81) Age, mean (SD): 55 (14.9) Disease duration, months, mean (SD): 10 (6.7) DAS28, mean (SD): 5.7 (0.9) Recruitment: All were outpatients attending the rheumatology units of the Hospital Clinic of Barcelona or the Hospital Parc Tauli of Sabadell between 1998 and 2003 and were followed for 2 years. After inclusion, all patients were treated according to a therapeutic protocol, with early introduction of DMARDs using a step-up approach. In all cases, intramuscular sodium aurothiomalate at a dose of 50 mg/week (25 mg/week during the first 2 weeks) was prescribed as first-choice DMARD together with methylprednisolone 4 mg/day. DMARD use at 2 year follow-up: gold salts: 28.6%, gold salts and methotrexate: 10.5%, methotrexate: 21.9%, methotrexate and other DMARDs (different from gold): 12.4%, other DMARDs 10.5% (leflunomide: 5.7%, leflunomide and infliximab: 1.9%, etanercept: 1.0%, ciclosporin A: 1.0%, hydroxychloroquine: 1.0%), no DMARDs: 14.3%
Prognostic variable(s)	CRP, ESR, RF+, anti-CCP+, Larsen score
Confounders	Univariate analysis considered above variables plus: sex, age, disease duration, HLA-DRB*04, shared epitope, shared epitope homozygous, haemoglobin, 28 tender joint count, 28 swollen joint count, VAS pain, DAS28 (continuous), mHAQ (continuous), erosion joint count
Outcomes and effect sizes	Outcome: radiographic progression at 2 years (defined as increase in Larsen score >4 units) Variables entered into model: haemoglobin, ESR, female gender, shared epitope, shared epitope homozygosity, HLA-DRB1*04 genotype, anti-CCP antibodies All marginally significant variables ($p<0.25$) in the univariate analysis were entered into the multivariate analysis (stepwise logistic regression model) as independent variables. The sensitivity, specificity, and positive and negative predictive values of the final multivariate model were also analysed. For all test, statistical significance was set at $p\leq0.05$. Results: Final model included female gender and DRB1*04. Anti-CCP+: OR 3.63 (95% CI 0.91 – 14.46)

Reference	Sanmarti 2007[157]
	Other prognostic factors (ESR, CRP, RF, erosion at first presentation) were not independently associated with the outcome.
Comments	Low risk of bias

1

2

Appendix E: Forest plots

Note: All factors are displayed on the forest plots even where odds ratios were not reported, as all factors were considered by all studies. Where a study has its results listed as 'Not estimable' for a specific factor, that factor was not independently associated with the outcome following multivariable analysis.

E.17 Prognostic factors for poor function

Figure 2: RF+ as prognostic factor for poor function (mHAQ > 0 at 2 years)

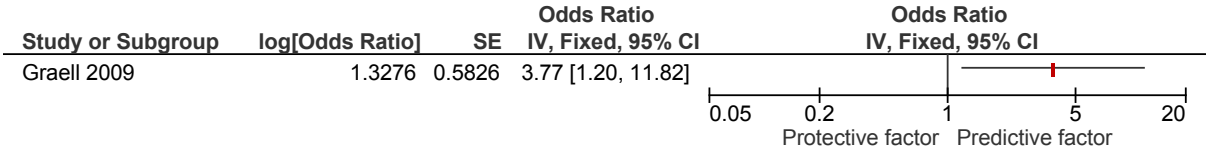


Figure 3: mHAQ (>0.5) as prognostic factor for poor function (mHAQ > 0 at 2 years)

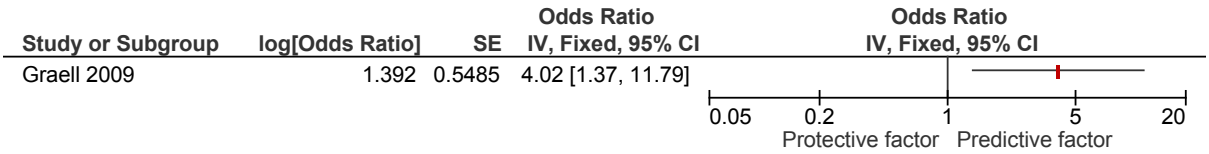


Figure 4: mHAQ (continuous) as prognostic factor for poor function (mHAQ > 0 at 2 years)

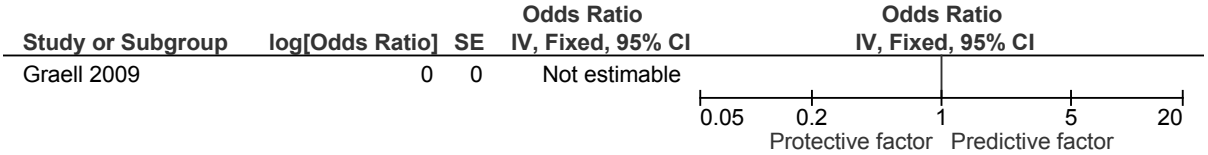


Figure 5: Anti-CCP+ as prognostic factor for poor function (mHAQ > 0 at 2 years)

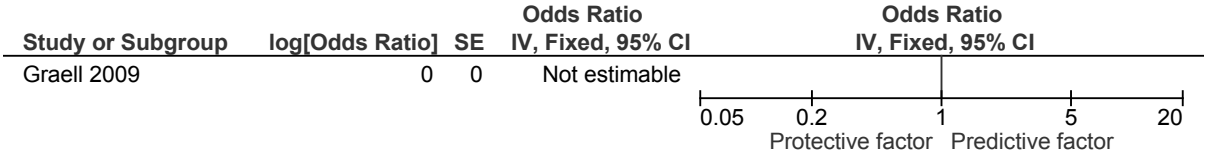


Figure 6: Baseline ESR as prognostic factor for poor function (mHAQ > 0 at 2 years; dichotomous)

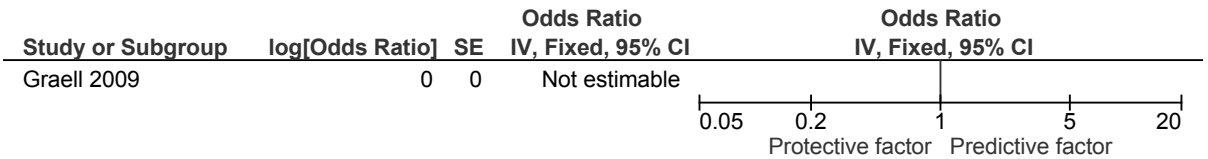


Figure 7: Baseline CRP as prognostic factor for poor function (mHAQ > 0 at 2 years)

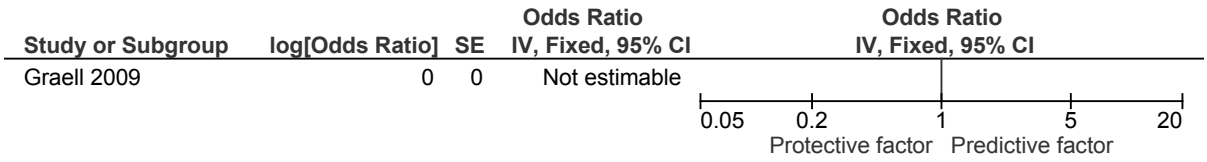
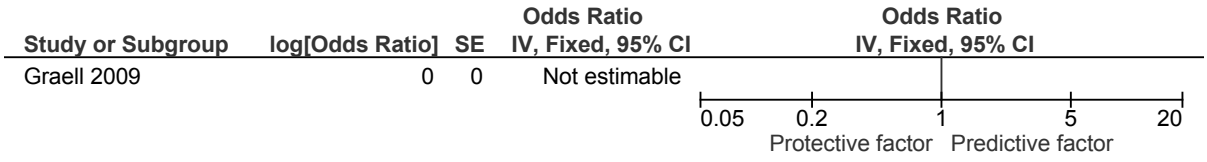


Figure 8: Baseline radiographic damage as prognostic factor for poor function (mHAQ > 0 at 2 years)



E.21 Prognostic factors for radiological progression

Figure 9: RF+ as prognostic factor for radiological progression (dichotomous)

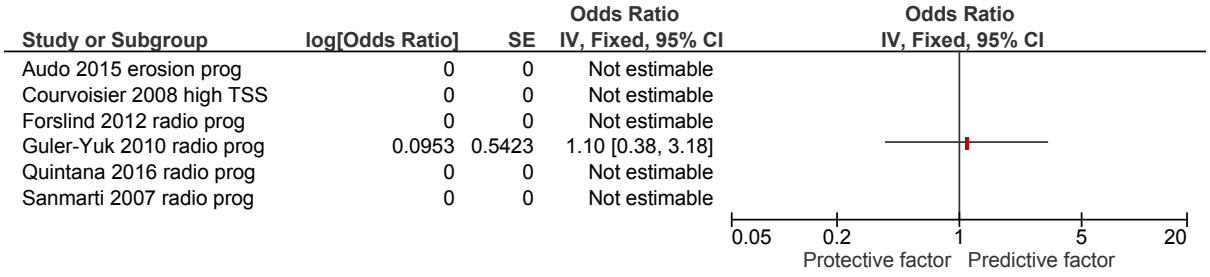


Figure 10: Anti-CCP+/ACPA+ as prognostic factor for radiological progression (dichotomous)

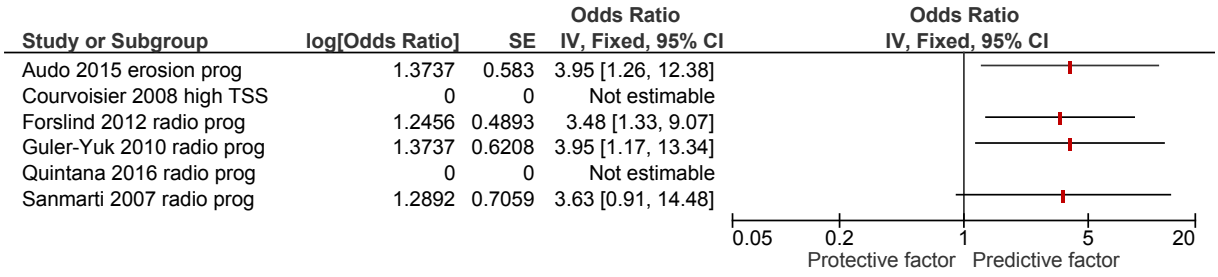


Figure 11: Baseline ESR as prognostic factor for radiological progression (dichotomous)

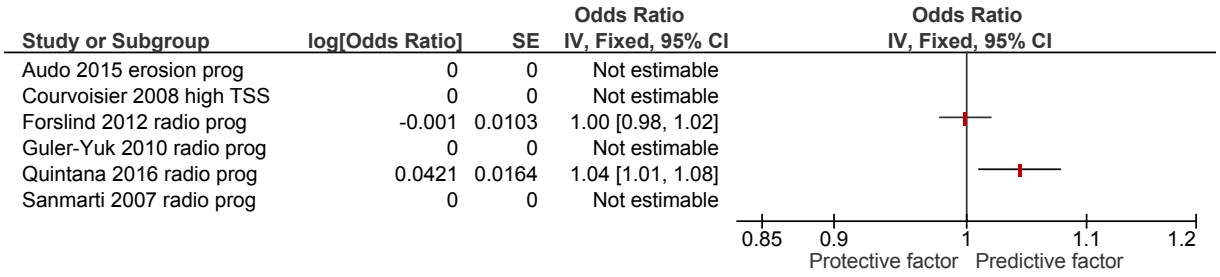


Figure 12: Baseline CRP as prognostic factor for radiological progression (dichotomous)

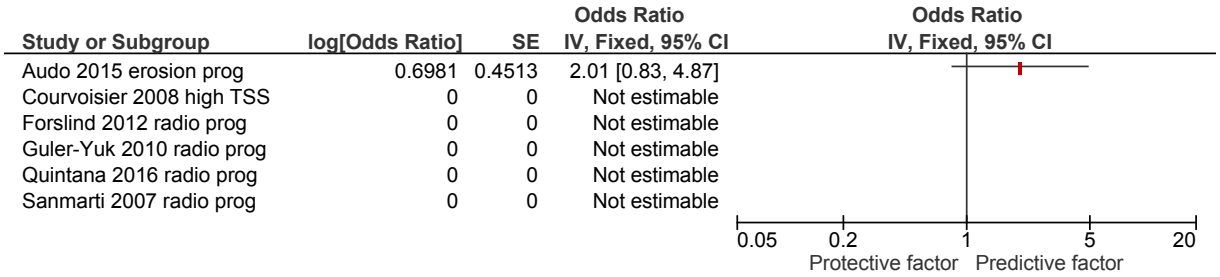
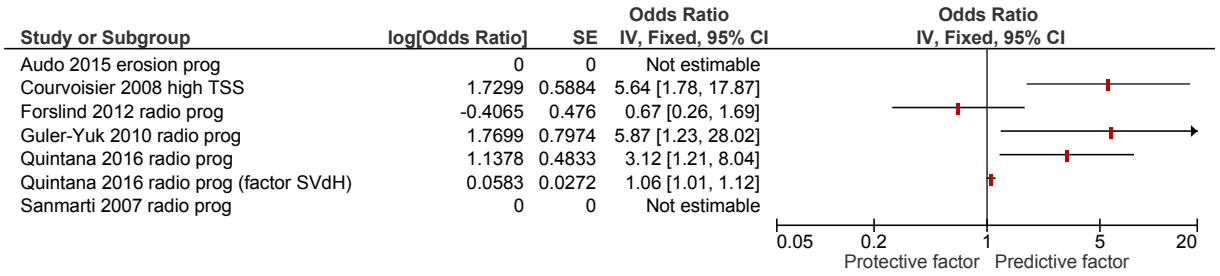


Figure 13: Baseline radiographic damage as prognostic factor for radiological progression (dichotomous)



Appendix F: GRADE tables

Table 14: Clinical evidence profile: Poor function (risk factors for predicting mHAQ > 0 at 2 years)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Baseline RF+								
1	Cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted OR: 3.772 (1.204 – 11.813)	LOW
Baseline MHAQ (>0.5)								
1	Cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted OR: 4.023 (1.1373 – 11.783)	LOW
Baseline MHAQ (continuous)								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline anti-CCP+								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline ESR								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline CRP								
1	Cohort	n/a	n/a	n/a	n/a	n/a	Not independently associated with the	n/a

	studies						outcome following multivariable analysis.	
Baseline Larsen score								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a

[1] Downgraded by 1 increment because the majority of the evidence was high risk of bias
n/a: unable to assess as data not reported (factor not independently associated with the outcome following multivariable analysis)

Table 15: Clinical evidence profile: Radiographic progression (dichotomous – various measures)

Quality assessment							Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Pooled effect (95% CI)**	
Baseline RF+								
1	Cohort studies	no serious risk of bias	no serious inconsistency	serious[4]	serious[1]	none	Adjusted OR: 1.10 (0.38 – 3.18)	LOW
5	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline anti-CCP+								
4	Cohort studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted OR: 3.95 (1.26 – 12.38) Adjusted OR: 3.48 (1.33 – 9.07) Adjusted OR: 3.95 (1.17 – 13.34) Adjusted OR: 3.63 (0.91 – 14.48)	MODERATE
2	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline ESR								

2	Cohort studies	serious[2]	no serious inconsistency	serious[4]	no serious imprecision	none	Adjusted OR: 1.00 (0.98 – 1.02) Adjusted OR: 1.04 (1.01 – 1.08)	LOW
4	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline CRP								
1	Cohort studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	Adjusted OR: 2.01 (0.83 – 4.87)	VERY LOW
5	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline radiographic damage								
4	Cohort studies	serious[2]	serious[3]	serious[4]	serious[1]	none	Adjusted OR: 5.46 (1.78 – 17.87) Adjusted OR: 0.67 (0.26 – 1.69) Adjusted OR: 5.87 (1.23 – 28.02) Adjusted OR: 3.12 (1.23 – 8.04) Adjusted OR: 1.06 (1.01 – 1.12)[5]	VERY LOW
2	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a

[1] Downgraded by 1 increment because the confidence interval crosses the line of no effect
[2] Downgraded by 1 increment because the majority of the evidence was high risk of bias or 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment because the effect estimates across studies appear both above and below the line of no effect
[4] Downgraded by 1 increment because at least one of the statistical analyses is indirect (inclusion of non-baseline factors in regression model)
[5] Same study as statistic immediately above, investigating continuous rather than dichotomous baseline radiological damage
n/a: unable to assess as data not reported (factor not independently associated with the outcome following multivariable analysis)

Table 16: Clinical evidence profile: Radiographic progression (continuous – change in total Sharp score at 2 years)

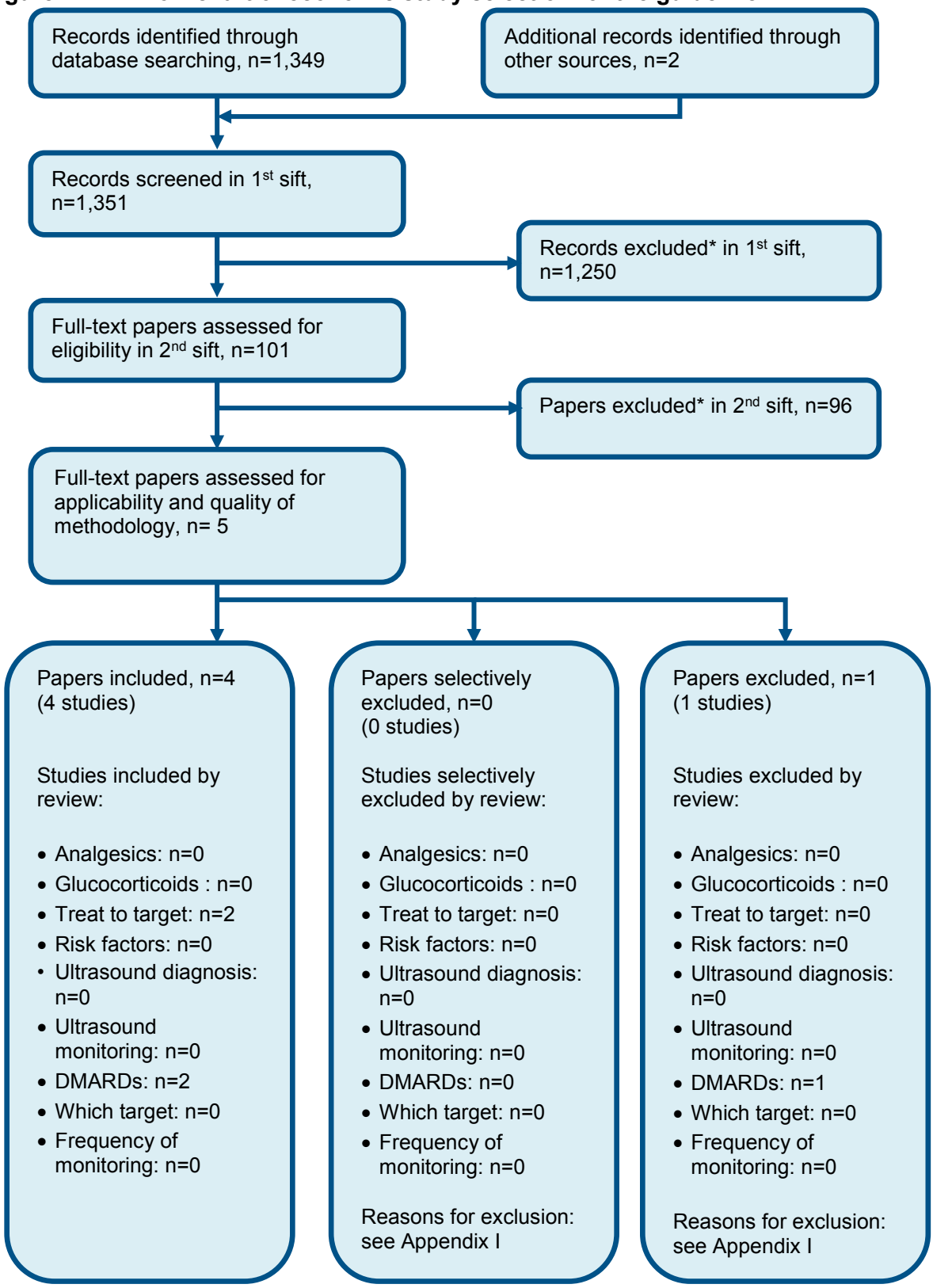
Quality assessment	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Baseline RF+								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline anti-CCP+								
1	Cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	Coefficient: 2.94 (-0.1 – 5.98)	MODERATE
Baseline ESR								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline CRP								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	n/a
Baseline total Sharp score								
1	Cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	Coefficient: 0.09 (-0.05 – 0.22)	MODERATE

[1] Downgraded by 1 increment because the confidence interval crosses the line of no effect
n/a: unable to assess as data not reported (factor not independently associated with the outcome following multivariable analysis)

Appendix G: Health economic evidence selection

Figure 14: Flow chart of economic study selection for the guideline



** Non-relevant population, intervention, comparison, design or setting; non-English language*

1
2

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 17: Studies excluded from the clinical review

Reference	Reason for exclusion
Ahlmen 2010[2]	Not adjusted for all key confounders.
Andersson 2013[3]	Wrong prognostic factors
Baillet 2015[5]	Not adjusted for all key confounders.
Baker 2016[6]	Not adjusted for all key confounders.
Baker 2014[7]	Not adjusted for all key confounders.
Balsa 2010[8]	Unclear whether population DMARD-treated.
Bansback 2006[9]	Not adjusted for all key confounders.
Barouta 2016[11]	Unclear whether population DMARD-treated. Unclear whether adjusted for all key confounders. Study design unclear (case control).
Benbouazza 2011[12]	DMARD-treated population.
Berglin 2006[13]	Not adjusted for all key confounders.
Berglin 2003[14]	Not adjusted for all key confounders.
Bjork 2007[15]	Not adjusted for all key confounders.
Black 2014[16]	Not adjusted for all key confounders.
Boman 2017[17]	Unclear whether any participants were DMARD treated at baseline
Bouman 2017[18]	Not adjusted for all key confounders.
Boyesen 2011[19]	DMARD-treated population.
Boyesen 2009[21]	DMARD-treated population.
Boyesen 2011[20]	Unclear whether population DMARD-treated.
Breedveld 2005[22]	DMARD-treated population.
Camilleri 2001[23]	Not adjusted for all key confounders.
Carpenter 2017[24]	Not adjusted for all key confounders.
Chen 2017[25]	Not adjusted for all key confounders.
Combe 2013[29]	Population not satisfying validated classification criteria for RA
Combe 2003[27]	Not adjusted for all key confounding factors
Combe 2001[28]	Not adjusted for all key confounders
Contreras-Yanez 2011[30]	DMARD-treated population.
Coste 1997[31]	DMARD-treated population.
da Mota 2012[35]	Not adjusted for all key confounders.
da Mota 2012[34]	Population doesn't satisfy validated classification criteria. Not adjusted for all key confounders.
Davis 2015[36]	DMARD-treated population.
De Cock 2014[37]	No multivariate analysis
de Miguel 2017[38]	Unclear whether any participants were DMARD treated at baseline
de Punder 2015[39]	Not adjusted for all key confounders.
de Vries-Bouwstra 2008[40]	Not adjusted for all key confounders.
Degboe 2015[41]	Not adjusted for all key confounders.
Deighton 1992[42]	Not adjusted for all key confounders.

Reference	Reason for exclusion
den Broeder 2002[43]	Not adjusted for all key confounders.
Dixey 2004[45]	Not adjusted for all key confounders.
Dohn 2011[46]	DMARD-treated population.
Drossaers-Bakker 2002[47]	Not adjusted for all key confounders.
Drouin 2010[48]	Not primary research. Prognostic studies checked for inclusion in this review.
Eberhardt 1995[49]	Not adjusted for all key confounders.
Ellingsen 2014[50]	Not adjusted for all key confounders.
Euesden 2017[51]	Outcome was not relevant to this research question
Fautrel 2015[52]	Not adjusted for all key confounders.
Fex 1996[53]	Not adjusted for all key confounders.
Fisher 2011[54]	No multivariable analysis
Forslind 2009[56]	Earlier report on a subgroup of an included study's population
Forslind 2004[55]	Earlier report on a subgroup of an included study's population
Forslind 2004[59]	Not adjusted for all key confounders.
Forslind 2003[58]	Not adjusted for all key confounders.
Forslind 2001[60]	Not adjusted for all key confounders.
Funck-Brentano 2013[61]	Population doesn’t satisfy validated classification criteria.
Galil 2016[62]	Unclear whether adjusted for all key confounders
Gandjbakhch 2014[63]	DMARD-treated population.
Garnero 2008[65]	Not adjusted for all key confounders.
Garnero 2002[64]	Not adjusted for all key confounders.
Glinatsi 2017[66]	Not adjusted for all key confounders.
Gomez-Vaquero 2016[67]	Not adjusted for all key confounders.
Goronzy 2004[68]	Not adjusted for all key confounders.
Grandaunet 2011[70]	A number of the population were DMARD-treated at baseline
Guillemin 2003[71]	Not adjusted for all key confounders.
Hambardzumyan 2016[74]	Not adjusted for all key confounders.
Hambardzumyan 2015[73]	Not adjusted for all key confounders.
Hammer 2010[75]	DMARD-treated population.
Harvey 2000[76]	Not adjusted for all key confounders.
Hashimoto 2009[77]	Not adjusted for all key confounders.
Hetland 2010[79]	Not adjusted for all key confounders.
Hoff 2009[81]	Not adjusted for all key confounders.
Hoff 2009[80]	DMARD-treated population.
Humphreys 2015[82]	Abstract only
Innala 2008[84]	DMARD-treated population.
Jansen 2001[85]	Not adjusted for all key confounders.
Jantti 2000[86]	Not adjusted for all key confounders.
Jawaheer 2010[87]	Not adjusted for all key confounders.
Joo 2017[88]	Majority of participants were DMARD treated at baseline
Kaltenhauser 2007[89]	Not adjusted for all key confounders.
Kaltenhauser 2001[90]	Not adjusted for all key confounders.
Kapetanovic 2015[91]	Not adjusted for all key confounders.
Karlson 2008[92]	Not adjusted for all key confounders.
Karpouzas 2017[93]	Majority of participants were DMARD treated at baseline

Reference	Reason for exclusion
Kastbom 2004[94]	DMARD-treated population.
Kaufmann 2003[95]	Not adjusted for all key confounders.
Khanna 2005[96]	Not adjusted for all key confounders.
Koga 2016[97]	DMARD-treated population.
Koga 2017[98]	Majority of participants were DMARD treated at baseline
Kondo 2017[99]	Multivariate analysis not adjusted for all key confounders.
Krabben 2015[100]	Review, not primary research. Assessed biomarkers for predicting radiological progression.
Kroot 2000[101]	Not adjusted for all key confounders.
Kuru 2009[102]	Unclear whether adjusted for all key confounders. Unclear whether population DMARD-treated.
Lee 2011[103]	A number of the population were DMARD-treated at baseline
Leigh 1992[104]	Not adjusted for all key confounders.
Liao 2011[105]	DMARD-treated population.
Lin 2003[106]	Unclear whether population DMARD-treated. Not adjusted for all key confounders
Lindqvist 2003[108]	Not adjusted for all key confounders.
Lindqvist 2002[109]	Not adjusted for all key confounders.
Lindqvist 2005[107]	Not adjusted for all key confounders.
Linn-Rasker 2007[110]	Not adjusted for all key confounders.
Machold 2007[111]	Not adjusted for all key confounders.
Maillefert 2004[112]	Not adjusted for all key confounders.
Manfredsdottir 2006[113]	Not adjusted for all key confounders. DMARD-treated population.
Manivel 2017[114]	Not adjusted for all key confounders.
Mathsson 2008[115]	No multivariable analysis
Matsushita 2016[116]	DMARD-treated population.
McQueen 2003[117]	DMARD-treated population.
Mewar 2006[118]	The majority of the included participants were DMARD-treated
Meyer 2006[120]	Not adjusted for all key confounders.
Meyer 2003[119]	Unclear whether population DMARD-treated. Unclear whether adjusted for all key confounders.
Michaud 2011[121]	Not adjusted for all key confounders.
Miriovsky 2010[122]	DMARD-treated population.
Mohammed 2015[123]	DMARD-treated population.
Nakajima 2016[124]	DMARD-treated population.
Nakajima 2017[125]	Majority of participants were DMARD treated at baseline
Navarro-Compan 2015[127]	DMARD-treated population.
Nawata 2016[128]	DMARD-treated population.
Nieto-Colonia 2008[129]	Not adjusted for all key confounders.
Nissen 2010[130]	A number of the population were DMARD-treated at baseline
Norton 2014[131]	Not adjusted for all key confounders.
Odegard 2006[132]	Unclear whether population DMARD-treated. Not adjusted for all key confounders
Ornbjerg 2016[135]	Not adjusted for all key confounders.
Ornbjerg 2014[134]	Not adjusted for all key confounders.
Paimela 1995[136]	Not adjusted for all key confounders.
Park 2011[137]	Not adjusted for all key confounders.

Reference	Reason for exclusion
Park 2016[138]	A number of the population were DMARD-treated at baseline
Pascual-Ramos 2009[139]	Unclear DMARD-treatment at baseline
Pease 1999[140]	Not adjusted for all key confounders.
Plant 2011[141]	Multivariate analysis in people with inflammatory polyarthritis
Prodanovic 2016[142]	Abstract only
Quinn 2006[143]	Not adjusted for all key confounders.
Ranganath 2008[145]	Not adjusted for all key confounders.
Reeback 1984[146]	Not adjusted for all key confounders.
Reneses 2009[147]	Not adjusted for all key confounders.
Richi 2002[148]	Not adjusted for all key confounders.
Rojas-Villarraga 2009[149]	The majority of the included participants were DMARD-treated
Ronnelid 2005[150]	Unclear whether population DMARD treated. Unclear whether adjusted for all key confounders.
Rooney 2010[151]	Did not account for key confounders using multivariate analysis
Rupp 2006[152]	Not adjusted for all key confounders.
Ruyssen-Witrand 2015[153]	Not adjusted for all key confounders.
Saeki 2013[154]	Not adjusted for all key confounders.
Saevarsdottir 2015[155]	Not adjusted for all key confounders.
Salaffi 2011[156]	Unclear whether adjusted for all key confounders
Sanmarti 2003[158]	Earlier report on a subgroup of an included study's population
Sanmarti 2009[159]	No multivariable analysis
Sherrer 1986[160]	Not adjusted for all key confounders.
Shi 2011[161]	Not prognostic study
Smolen 2006[162]	Not adjusted for all key confounders.
Soderlin 2011[163]	Multivariate analysis using EULAR response as an outcome
Stockman 1991[164]	DMARD-treated population.
Svensson 2010[165]	Not adjusted for all key confounders.
Syversen 2010[169]	DMARD-treated population.
Syversen 2010[168]	DMARD-treated population.
Syversen 2008[166]	DMARD-treated population.
Syversen 2009[167]	A number of the population were DMARD-treated at baseline
Tamai 2017[170]	Not adjusted for all key confounders.
Tanaka 2005[171]	Not adjusted for all key confounders.
Tobon 2013[172]	Mixed arthritis population
Twigg 2017[175]	Not adjusted for all key confounders.
Twigg 2017[174]	Could not be obtained
Valenzuela-Castano 2000[176]	Not adjusted for all key confounders.
van den Broek 2013[178]	Not adjusted for all key confounders.
van den Broek 2012[177]	Not adjusted for all key confounders.
van der Heide 1995[179]	Not adjusted for all key confounders.
van der Heijde 1992[180]	Not adjusted for all key confounders.
van der Kooi 2011[181]	Not adjusted for all key confounders.
van der Linden 2009[182]	Not adjusted for all key confounders.
van der Linden 2009[183]	Not adjusted for all key confounders.
van der Woude 2010[184]	Not adjusted for all key confounders.
van Leeuwen 1995[186]	Not adjusted for all key confounders.

Reference	Reason for exclusion
van Leeuwen 1993[185]	No multivariate analysis
van Nies 2015[187]	Not adjusted for all key confounders.
van Steenbergen 2015[188]	Not adjusted for all key confounders.
van Steenbergen 2015[189]	Not adjusted for all key confounders.
van Tuyl 2010[190]	Not adjusted for all key confounders.
van Zeben 1993[191]	Not adjusted for all key confounders.
Vastesaeger 2009[192]	DMARD-treated population.
Vencovsky 2003[193]	Not adjusted for all key confounders.
Visser 2010[194]	Combined CCP and RF factors.
Vittecoq 2003[195]	DMARD-treated population.
Wagner 2007[196]	DMARD-treated population.
Wechalekar 2016[197]	Not adjusted for all key confounders.
Welsing 2001[198]	Not adjusted for all key confounders.
Wevers-de Boer 2015[199]	Mixed arthritis population
Wiles 2000[200]	Not adjusted for all key confounders.
Winfield 1983[201]	Population doesn't satisfy validated classification criteria.
Wolfe 1998[202]	DMARD-treated population.
Yamazaki 2016[203]	
Young 1988[205]	Not adjusted for all key confounders.
Young-Min 2007[204]	Unclear whether population DMARD-treated. Not adjusted for all key confounders
Zavada 2017[206]	Not adjusted for all key confounders.

I.21 Excluded health economic studies

Table 18: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.14 Managing poor prognosis RA

Research question: What is the clinical and cost effectiveness of managing RA with a poor prognosis (identified as presence of anti-CCP antibodies or evidence of erosions on X-ray at diagnosis) with a different strategy from that used for standard management of RA?

Why this is important:

Current recommendations suggest all people with RA should be offered the same standard therapy; however clinical experience suggests that some people respond less well and some suffer progressive radiographic damage and impaired function despite standard treatment. Several factors have been identified in the literature that, if present and identified early in the course of the disease, may predict a poor prognosis (greater radiographic progression) compared to RA without presence of these factors. These include anti-CCP antibody positivity and the presence of radiographic erosions at baseline. It remains unclear however if people with poor prognostic markers should be managed differently early in the disease,

and whether a different approach would improve radiographic and functional (HAQ) outcomes in this cohort.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with rheumatoid arthritis identified as having poor prognosis Intervention(s): Standard treatment Comparison: Intensive treatment regime Outcome(s):Radiographic progression, function (e.g. HAQ), disease activity, quality of life
Importance to patients or the population	Identifying a different management strategy for a subgroup of people with RA who are at higher risk of radiographic progression could lead to more personalised management decisions and improve longer term outcomes for these people.
Relevance to NICE guidance	New evidence would have direct impact on future updates of this NICE guideline if a different management strategy is identified as being more effective in this group.
Relevance to the NHS	The cost effectiveness of managing people with RA and poor prognostic markers differently is unknown. However, persistent disease activity despite therapy is costly for people with RA, the NHS, and wider society due to poor functional outcomes, use of high-cost drugs and impact on work and caring responsibilities. More effective management of this cohort early in the course of disease may be cost effective in the longer term if radiographic damage and poor functional outcomes can be averted or delayed. Employing a stratified approach to management of this high risk group could reduce the use of more costly therapies later in the disease, reduce the need for joint replacement surgery, and enable people with RA to continue living independent and productive lives.
National priorities	The NIHR identified stratified medicine as a key area of development in 2014 (NIHR Stratified Medicine Capabilities, 2014) and funding to develop stratified medicine studies is a key priority of all national research councils and rheumatology charities. Implementing the findings of these studies into clinical practice will be a challenge and opportunity for the NHS, but is likely to be a key route to improving outcomes in RA. The ability to better manage RA with poor prognostic markers would help deliver this national priority.
Current evidence base	As the evidence review in chapter B demonstrates, although independent markers of poor prognosis have been identified in the literature and are collected in routine practice (radiographic erosions at baseline and ACPA positivity), there is a lack of high-quality evidence on whether or how this group should be managed differently. Equally, there was no clinical trial data identified within the guideline reviews to assess the impact of any novel management approach that would help guide the clinical and cost effectiveness of such an approach.
Equality	Not applicable/none
Study design	Accepting the prognostic factors identified from the reviews undertaken in this guideline, the study design should ideally be a randomised clinical trial of two treatment approaches (standard versus intensive) in patients with poor prognostic factors. There would have to be a pragmatic element to the trial design, accepting that choice of treatment may differ slightly within groups (as it would be tailored to the individual), but the intensity and range of drugs used would differ between groups. The outcomes of any study should include radiographic progression, functional status (for example, HAQ), disease activity and quality of life, so that an assessment of cost effectiveness can occur.
Feasibility	The studies are feasible to conduct, but therapies may need funding

	outside of normal NHS funding streams, as intensive therapies may include high-cost drugs outside of current NICE guidance.
Other comments	A key population that is relevant to other NICE Technology Appraisal process is patients with moderate disease activity (DAS28 <5.1) but poor prognostic markers. TA 375 felt there was insufficient evidence to support the use of high-cost therapies in patients with moderate disease, based in part due to a lack of data on poor prognostic markers. Large-scale UK-based academic consortia are currently investigating similar research questions (for example, MATURA).
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

1