

Rheumatoid arthritis in adults: diagnosis and management

Evidence review B Risk factors

NICE guideline NG100

Prognostic evidence review

July 2018

Final

*This evidence review was developed by
the National Guideline Centre*

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ISBN: 978-1-4731-3003-6

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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	<ul style="list-style-type: none"> • 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) <p>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.</p>
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 early 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) Mean MHAQ at baseline: 0.97	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 (n=105)	Adjusted OR: 3.772 (1.204 – 11.813) at 2 years	No serious imprecision	LOW
Baseline mHAQ (>0.5)	1 (n=105)	Adjusted OR: 4.023 (1.373 – 11.783) at 2 years	No serious imprecision	LOW
Baseline mHAQ (continuous)	1 (n=105)	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline anti-CCP+	1 (n=105)	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline ESR	1 (n=105)	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline CRP	1 (n=105)	Not independently associated with the outcome following multivariable analysis.	n/a	n/a
Baseline Larsen score	1 (n=105)	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 2016³³

(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 suggested baseline RF positivity was independently associated with a mHAQ of greater than 0 at 2 years. Evidence on the association between was inconsistent across risk factors 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 **Error! Reference source not found.**, **Error! Reference source not found.** and 2.9.

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	<ul style="list-style-type: none">• 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) <p>All factors should be measured at baseline. People should not be receiving DMARD treatment at the time of measurement.</p>
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)

See appendix D for full evidence tables.

2.5.4 Quality assessment of clinical studies included in the evidence review

Table 7: Clinical evidence summary: Radiographic progression at 1 to 10 years (dichotomous – various measures)

Risk factor for predicting radiographic progression	Number of studies ¹	Effect (95% CI)	Imprecision	GRADE Quality
Baseline RF+	1 (n=256)	Adjusted odds ratio (OR): 1.10 (0.38–3.18) at 1-4 years	Serious	LOW
	5 (n=1124)	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline anti-CCP+ / ACPA+	4 (n=1139)	Adjusted OR: 3.95 (1.26–12.38) at 2 years	No serious imprecision	MODERATE
		Adjusted OR: 3.48 (1.33–9.07) at 2 years		
		Adjusted OR: 3.95 (1.17–13.34) at 1-4 years		
	2 (n=241)	Adjusted OR: 3.63 (0.91–14.48) at 2 years	Serious	LOW
		Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline ESR	2 (n=508)	Adjusted OR: 1.00 (0.98–1.02) at 2 years	Serious	VERY LOW
		Adjusted OR: 1.04 (1.01–1.08) at 3 years	No serious imprecision	LOW
	4 (n=872)	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline CRP	1 (n=399)	Adjusted OR: 2.01 (0.83–4.87) at 2 years	Serious	VERY LOW
	5 (n=981)	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline radiographic damage	4 (n=876)	Adjusted OR: 5.64 (1.78–17.87) at 10 years	No serious imprecision	LOW
		Adjusted OR: 0.67 (0.26–1.69) at 2 years	Serious	VERY LOW

Risk factor for predicting radiographic progression	Number of studies ¹	Effect (95% CI)	Imprecision	GRADE Quality
		Adjusted OR: 5.87 (1.23–28.02) at 1-4 years	No serious imprecision	LOW
		Adjusted OR: 3.12 (1.23–8.04) at 3 years		
		Adjusted OR: 1.06 (1.01–1.12) ² at 3 years		
	2 (n=504)	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 (n=130)	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline anti-CCP+ / ACPA+	1 (n=130)	Coefficient: 2.94 (-0.1–5.98) at 2 years	Serious imprecision	MODERATE
Baseline ESR	1 (n=130)	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline CRP	1 (n=130)	Not independently associated with the outcome following multivariable analysis	n/a	n/a
Baseline total Sharp score	1 (n=130)	Coefficient: 0.09 (-0.05–0.22) at 2 years	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, low to moderate quality evidence, n=1139) and baseline radiographic damage (4 of 7 studies, low to very low quality evidence, n=876) were independently associated with radiographic progression at least 12 months later. The evidence on the other prognostic factors was similarly inconsistent though the studies typically did not find an independent association to the outcome. The following studies did not find the factors to be independently associated with subsequent radiographic progression: 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).

2.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

2.9 The committee's discussion of the evidence

2.9.1 Interpreting the evidence

2.9.1.1 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.

2.9.1.2 The quality of the evidence

Poor function

Data for poor function measured by HAQ were limited to a single study with 105 participants that considered all of the pre-specified prognostic factors of interest. Evidence for baseline RF+ status and baseline modified HAQ score greater than 0.5 as independent prognostic factors for modified HAQ greater than 0 at 2 years was considered to be low 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 people with quite different HAQ scores (anything over 0) applying similar influence on the regression analysis results, further limiting the evidence. The committee considered the study to be fairly well conducted but limited by the quantity of 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, assessed through visual inspection of the distributions, in the results between studies, with 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.

The committee considered the studies to be of varying quality but the breadth of the evidence gave confidence in the results of the review.

2.9.1.3 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

Radiographic progression was measured using Sharp score, Sharp van der Heijde score, and Larsen score with the change in score or varying cut-offs utilised.

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 update suggests 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

2.9.2 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 England¹⁰). 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 England¹⁰). 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.

2.9.3 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.

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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

Appendices

Appendix A: Review protocols

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)	<ul style="list-style-type: none"> • 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) <p>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).</p> <p>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).</p>
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)	<ul style="list-style-type: none"> Endnote will be used for bibliographies, citations, sifting and reference management
XIII	Information sources – databases and dates	<p>Databases: The databases to be searched are Medline and Embase Date limits for search: None Language: English</p> <p>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</p>
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.
XVI I	Search strategy – for one database	For details, please see appendix B
XVI II	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.
XXI I	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXI II	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXI V	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XX V	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XX VI	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
XX VII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XX VIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXI X	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XX X	PROSPERO registration number	Not registered

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)	<ul style="list-style-type: none"> • 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) <p>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).</p> <p>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).</p>
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Not applicable
VII	Outcomes and prioritisation	<p>Radiographic progression (continuous) at 12 months or more</p> <p>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).</p> <p>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</p>
VIII	Eligibility criteria – study design	<p>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.</p> <p>Retrospective cohort studies will be included only if no prospective cohort studies are identified.</p>
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.
XVI I	Search strategy – for one database	For details, please see appendix B
XVI II	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.
XXI I	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXI II	Meta-bias assessment – publication bias, selective	For details, please see section 6.2 of Developing NICE guidelines: the manual.

ID	Field	Content
	reporting bias	
XXI V	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XX V	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XX VI	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
XX VII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XX VIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXI X	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XX X	PROSPERO registration number	Not registered

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
	<p>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.</p> <p>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.</p> <p>If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both, then there is discretion over whether it should be included.</p> <p>Where there is discretion</p> <p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <p>UK NHS (most applicable).</p> <p>OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).</p> <p>OECD countries with predominantly private health insurance systems (for example, Switzerland).</p> <p>Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.</p> <p>Health economic study type:</p> <p>Cost–utility analysis (most applicable).</p> <p>Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).</p> <p>Comparative cost analysis.</p> <p>Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.</p> <p>Year of analysis:</p> <p>The more recent the study, the more applicable it will be.</p> <p>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’.</p> <p>Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations.</p> <p>Quality and relevance of effectiveness data used in the health economic analysis:</p> <p>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.</p>

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

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.2 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
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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

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)

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)

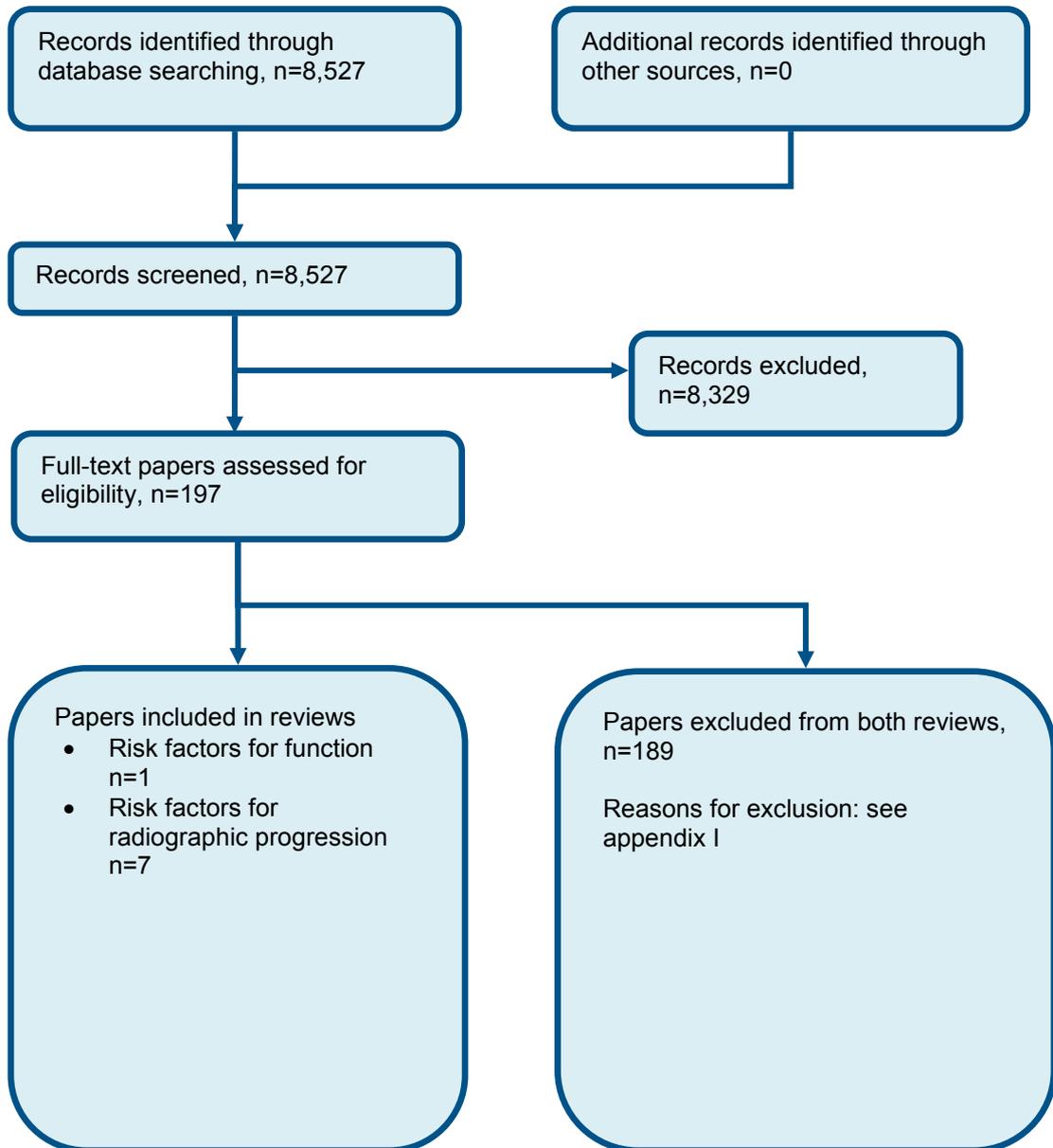
NHS EED and HTA (CRD) search terms

#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

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	<p>n=399 Country: France</p> <p>Prognostic factors (baseline) of 399 patients: RF+, n (%): 203 (51) ACPA+, n (%): 180 (45) Total modified Sharp score, mean (SD): 3.8 (4.4)</p> <p>Inclusion criteria: Patients of the ESPOR cohort who fulfilled the ACR-EULAR 2010 criteria for the classification of Rheumatoid arthritis (RA).</p> <p>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).</p> <p>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)</p>

Reference	Audo 2015 ⁴ , #2158
	<p>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.</p> <p>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).</p>
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	<p>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 (%)</p> <p>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.</p> <p>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.</p> <p>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)</p> <p>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).</p>

Reference	Audo 2015⁴, #2158
	<p>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).”</p> <p>“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.”</p>
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.)

Reference	Courvoisier 2008³²
Study type and analysis	Prospective cohort study Stepwise multiple logistic regression
Number of participants and characteristics	<p>n=191 (112 analysed) Country: France</p> <p>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)</p> <p>Inclusion criteria: Patients fulfilling the ACR criteria for the classification of RA for ≤ 1 year at the start of the study.</p> <p>Exclusion criteria: Patients previously treated with DMARDs.</p> <p>Population characteristics (baseline) of 112 patients: Female, n (%): 90 (80.3)</p>

Reference	Courvoisier 2008 ³²
	<p>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)</p> <p>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.</p> <p>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.</p> <p>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).</p>
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	<p>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)</p> <p>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.</p> <p>Results:</p>

Reference	Courvoisier 2008³²
	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)

Reference	Forslind 2012⁵⁷
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 recent 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
	<p>DMARD prescribed at baseline: none: 77 (20%), methotrexate: 155 (41%), sulfasalazine: 102 (27%), other DMARD: 44 (12%), combination: 1 (0%), biologics: 0 (0%)</p> <p>Recruitment: people consecutively enrolled in study at 6 centres in Sweden between 1993 and 1999.</p>
Prognostic variable(s)	RF+, anti-CCP+, ESR (continuous), CRP (continuous), Sharp score (continuous), presence of erosions
Confounders	<p>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.</p>
Outcomes and effect sizes	<p>Outcome: Radiographic progression: SvdH score change of >5.8 at 2 years. 145 (38%) progressed in 2 years</p> <p>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</p> <p>Variables significantly associated with radiographic progression in the univariate analysis were out into multiple regression analysis.</p> <p>Results:</p> <p>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</p> <p>Erosions at baseline: OR 0.666 (95% CI 0.262–1.691)</p> <p>Anti-CCP+: OR 3.475 (95% CI 1.332–9.066)</p> <p>ESR at baseline: OR 0.999 (95% CI 0.979–1.018)</p> <p>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.</p> <p>CRP at baseline was not independently associated with the outcome.</p>
Comments	<p>High risk of bias (study attrition – only 45% had radiographs suitable for inclusion at baseline and 1 year)</p> <p>Serious indirectness due to due to final model including multiple variables measured at 1 year.</p>

Reference	Graell 2009 ⁶⁹
Study type and analysis	Prospective cohort study Binary multivariate logistic regression
Number of participants and characteristics	<p>n=115 (105 analysed) Country: Spain</p> <p>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)</p> <p>Inclusion criteria: Patients fulfilling the ACR criteria for the classification of RA, with symptoms for < 24 months</p> <p>Exclusion criteria: Patients previously treated with DMARDs, prednisone, or equivalent at a dose > 10mg per day</p> <p>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)</p> <p>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%.</p> <p>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.</p>
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	<p>Outcome: Disability (MHAQ>0) at 2 years (77/105 patients experienced outcome)</p> <p>Variables entered into model: Specific variables not stated.</p> <p>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.</p> <p>Results:</p> <p>Final model included age, RF+ status, and baseline MHAQ (>0.5)</p> <p>RF+: OR 3.772 (95% CI 1.204 – 11.813)</p> <p>MHAQ > 0.5: OR 4.023 (95% CI 1.373 – 11.783)</p> <p>Other prognostic factors (ESR, CRP, Larsen score, MHAQ continuous) were not independently associated with the outcome</p>
Comments	Very high risk of bias (outcome cut-off, statistical analysis – methods unclear)

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	<p>n=272 (256 analysed)</p> <p>Country: the Netherlands</p> <p>Prognostic factors (baseline) of 256 patients:</p> <p>RF+, n (%): 159 (62%)</p> <p>ACPA +, n (%): 133 (62%; data on 247 patients, not all at baseline)</p> <p>ESR, mm/h, median (IQR): 37 (19-54)</p> <p>CRP, mg/dL, median (IQR): 20 (9-58)</p> <p>Total SHS score, mean (SD): 5.9 (8.2; data on 248 patients)</p> <p>Presence erosive damage ≥1 unit, n (%): 174 (70%; data on 248 patients)</p> <p>Inclusion criteria: Patients enrolled in the BeST trial (see recruitment below).</p>

Reference	Güler-Yüksel 2010 ⁷²
	<p>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.</p> <p>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)</p> <p>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.</p> <p>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.</p>
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/m ² , symptom duration ≥ 6 months, number of swollen joints ≥ 10 , Ritchie 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/cm ² (first follow-up variables were adjusted for treatment group and the use of intraarticular glucocorticoids injections and antiresorptive therapy).
Outcomes and effect sizes	<p>Outcome: Progressive total joint damage (≥ 5 units) between years 1-4 (77/256 patients experienced outcome)</p> <p>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.</p> <p>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.</p>

Reference	Güler-Yüksel 2010 ⁷²
	<p>Results:</p> <p>Final model included all variables entered into model (see above).</p> <p>ACPA+: OR 3.95 (95% CI 1.17 – 15.0)</p> <p>RF+: OR 1.10 (0.38 – 2.98)</p> <p>SHS \geq 1 unit (baseline): OR 5.87 (1.23 – 28.1)</p> <p>Other prognostic factors (ESR \geq 30 mm/h, CRP \geq 10 mg/L) were not independently associated with the outcome.</p> <p>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.</p>
Comments	<p>Low risk of bias.</p> <p>Serious indirectness (inclusion of variables measured at 1 year in final model).</p>

Reference	Hetland 2009 ⁷⁸
Study type and analysis	<p>Multicentre RCT: CIMESTRA</p> <p>Multiple linear regression</p>
Number of participants and characteristics	<p>n=160 (130 included in MRI sub-study analysed here)</p> <p>Country: Denmark</p> <p>Prognostic factors (baseline) of 130 people included in analysis</p> <p>IgM RF+ n (%): 67 (52%)</p> <p>Anti-CCP +: 61 (47%)</p> <p>ESR, mean (IQR): unclear</p> <p>CRP, mg/L, mean (IQR): Unclear</p> <p>Erosive disease: 62 (48%)</p> <p>Total Sharp score, mean (SD): 5.2 (6.8)</p> <p>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.</p> <p>Exclusion criteria: None detailed. Reasons for exclusion from MRI sub-study: contraindications for MRI (n=3), disease activity that did</p>

Reference	Hetland 2009 ⁷⁸
	<p>not allow for MRI (n=8), anxiety/claustrophobia (n=5), participant refusal (n=7), unknown (n=1)</p> <p>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.</p> <p>Recruitment: RCT recruiting consecutive patients from 5 rheumatology centres in Denmark from October 1999 to October 2002.</p>
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	<p>Outcome: Radiographic progression: change in TSS at 2 years. 39 (30%) progressed in 2 years</p> <p>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</p> <p>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)</p> <p>CRP, ESR, RF+ were not associated with the outcome in the univariate analysis.</p>
Comments	Low risk of bias

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	<p>n=159 (129 included in analysis due to withdrawal from study) Country: Columbia</p> <p>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%)</p> <p>Inclusion criteria: People with early onset rheumatoid arthritis (EORA). Disease duration <12 months. Fulfilling 1987 and 2010 ACR criteria for the classification of RA.</p> <p>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.</p> <p>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%).</p> <p>Recruitment: Attending rheumatology unit of the Universidad Nacional de Colombia or the Clinica de Artritis y Rehabilitacion (CAYRE).</p>
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 2016¹⁴⁴
	genotypes, Anti-SSA/Ro autoantibodies, Antinuclear Antibodies (ANAs), therapy utilised.
Outcomes and effect sizes	<p>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.</p> <p>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)</p> <p>Other prognostic factors (CRP, CCP, RF) were not independently associated with the outcome.</p>
Comments	High risk of bias (study participation – sampling time frame and recruitment not adequately described)

Reference	Sanmarti 2007¹⁵⁷
Study type and analysis	<p>Prospective cohort study Stepwise multivariate logistic regression</p>
Number of participants and characteristics	<p>n=115 (105 analysed) Country: Spain</p> <p>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)</p> <p>Inclusion criteria: Patients fulfilling the ACR criteria for the classification of RA, with symptoms for < 24 months.</p>

Reference	Sanmarti 2007 ¹⁵⁷
	<p>Exclusion criteria: Patients previously treated with DMARDs or prednisone or equivalent at a dose > 10 mg per day.</p> <p>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)</p> <p>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.</p> <p>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.</p> <p>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%</p>
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	<p>Outcome: radiographic progression at 2 years (defined as increase in Larsen score >4 units)</p> <p>Variables entered into model: haemoglobin, ESR, female gender, shared epitope, shared epitope homozygosity, HLA-DRB1*04 genotype, anti-CCP antibodies</p> <p>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≤0.05.</p> <p>Results: Final model included female gender and DRB1*04. Anti-CCP+: OR 3.63 (95% CI 0.91 – 14.46)</p>

Reference	Sanmarti 2007¹⁵⁷
	Other prognostic factors (ESR, CRP, RF, erosion at first presentation) were not independently associated with the outcome.
Comments	Low risk of bias

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.1 Prognostic factors for poor function

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

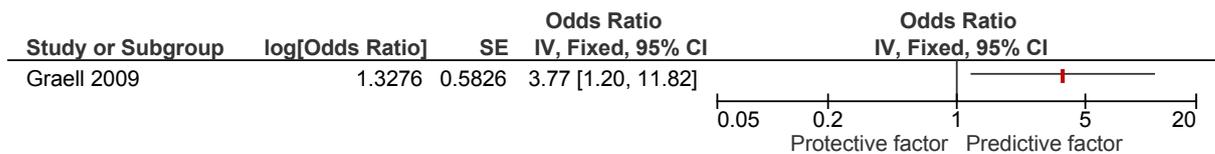


Figure 3: mHAQ (>0.5) as prognostic factor for poor function (mHAQ > 0 at 2 years)

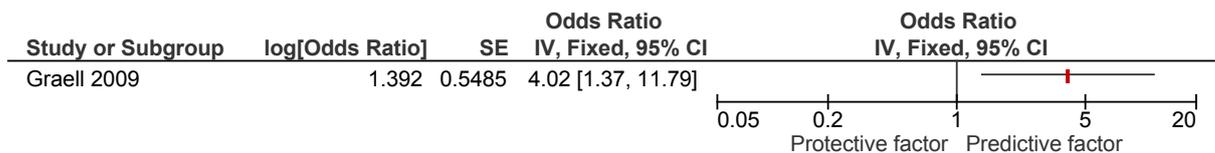


Figure 4: mHAQ (continuous) as prognostic factor for poor function (mHAQ > 0 at 2 years)

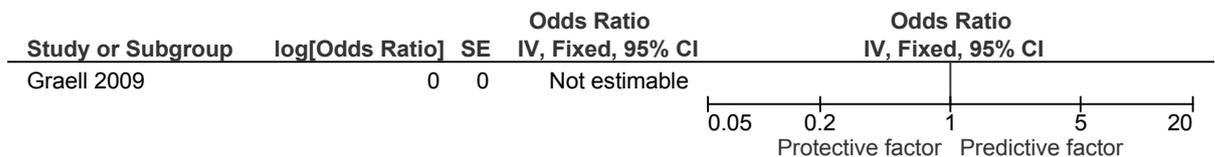


Figure 5: Anti-CCP+ as prognostic factor for poor function (mHAQ > 0 at 2 years)

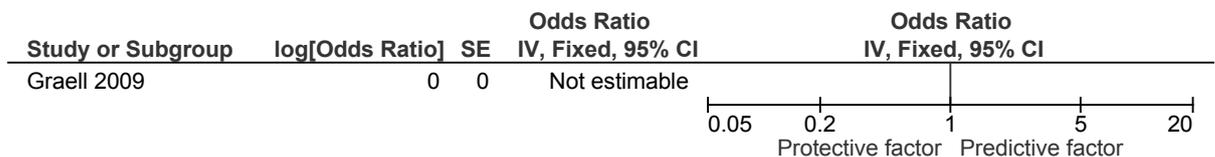


Figure 6: Baseline ESR as prognostic factor for poor function (mHAQ > 0 at 2 years; dichotomous)

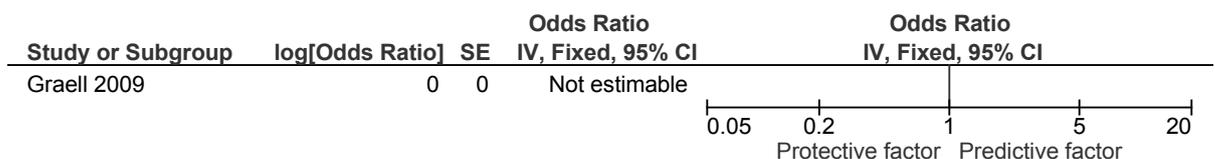


Figure 7: Baseline CRP as prognostic factor for poor function (mHAQ > 0 at 2 years)

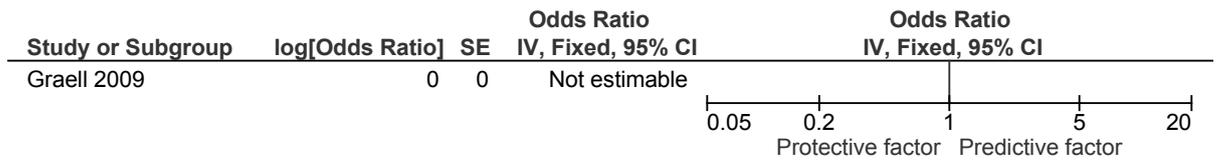
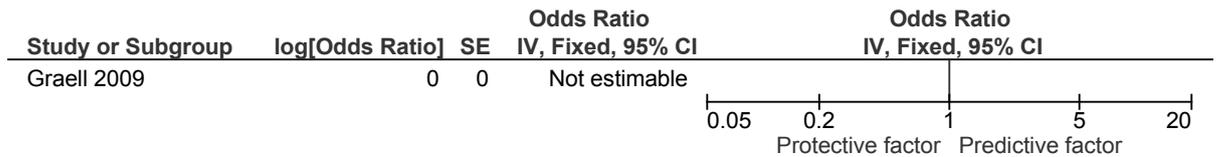


Figure 8: Baseline radiographic damage as prognostic factor for poor function (mHAQ > 0 at 2 years)



E.2 Prognostic factors for radiological progression

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

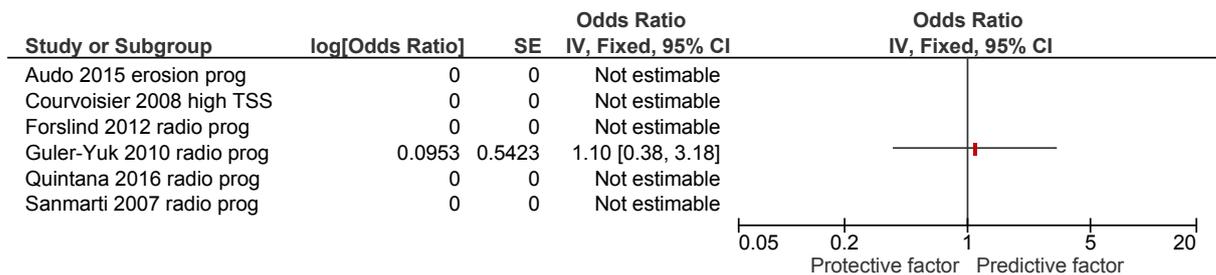


Figure 10: Anti-CCP+/ACPA+ as prognostic factor for radiological progression (dichotomous)

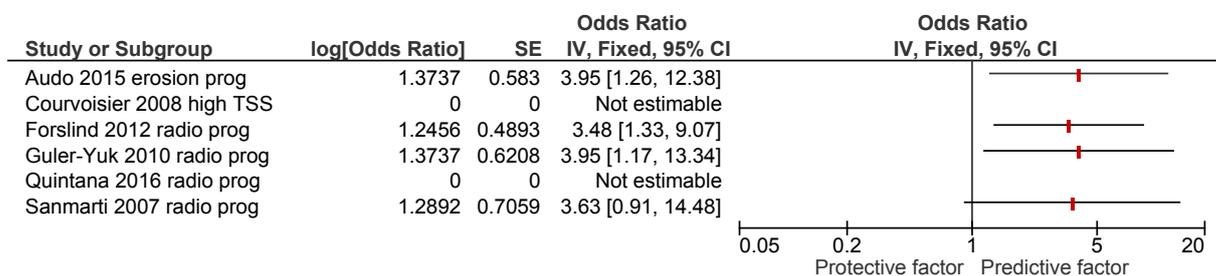


Figure 11: Baseline ESR as prognostic factor for radiological progression (dichotomous)

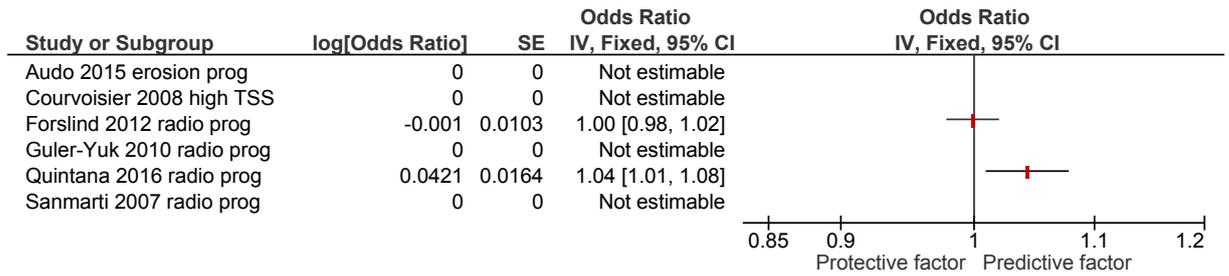


Figure 12: Baseline CRP as prognostic factor for radiological progression (dichotomous)

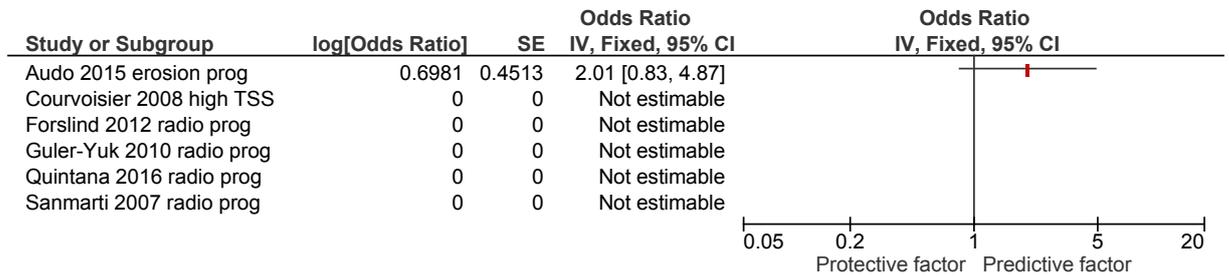
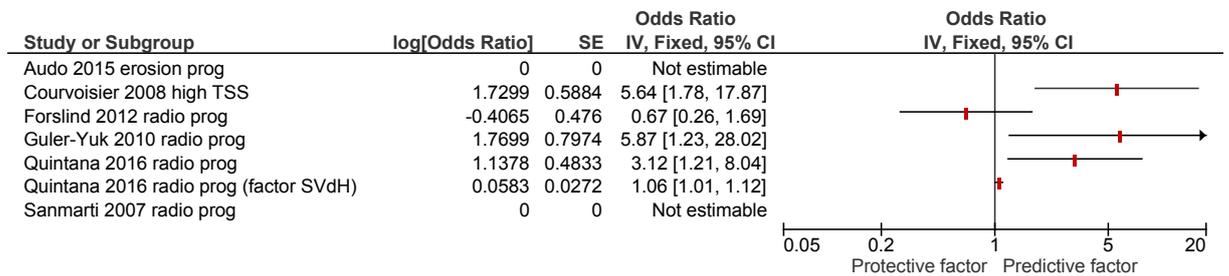


Figure 13: Baseline radiographic damage as prognostic factor for radiological progression (dichotomous)



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)	MODERATE
							Adjusted OR: 3.48 (1.33 – 9.07)	
							Adjusted OR: 3.95 (1.17 – 13.34)	
					Serious ¹	Adjusted OR: 3.63 (0.91 – 14.48)	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
Baseline ESR								

2	Cohort studies	serious ²	no serious inconsistency	serious ⁴	no serious imprecision	none	Adjusted OR: 1.00 (0.98 – 1.02)	LOW
							Adjusted OR: 1.04 (1.01 – 1.08)	
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	No serious imprecision	none	Adjusted OR: 5.64 (1.78 – 17.87)	LOW
					serious ¹		Adjusted OR: 0.67 (0.26 – 1.69)	VERY LOW
					No serious imprecision		Adjusted OR: 5.87 (1.23 – 28.02)	LOW
							Adjusted OR: 3.12 (1.23 – 8.04)	
							Adjusted OR: 1.06 (1.01 – 1.12) ⁵	
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
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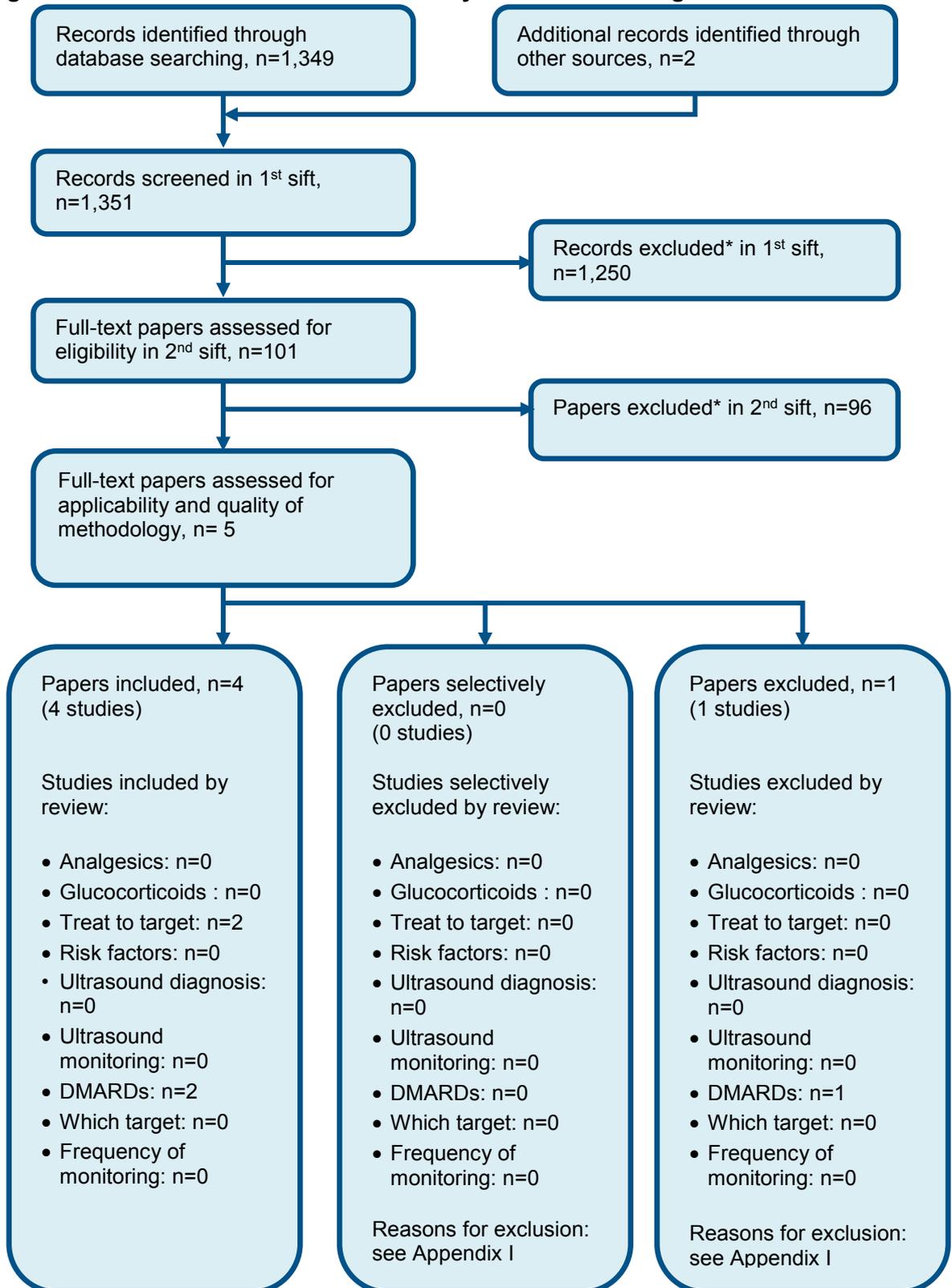
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Baseline RF+								
1	Cohort studies	n/a	n/a	n/a	n/a	n/a	Not independently associated with the outcome following multivariable analysis.	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*

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.
den Broeder 2002 ⁴³	Not adjusted for all key confounders.

Reference	Reason for exclusion
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.
Karpouzias 2017 ⁹³	Majority of participants were DMARD treated at baseline
Kastbom 2004 ⁹⁴	DMARD-treated population.

Reference	Reason for exclusion
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.
Park 2016 ¹³⁸	A number of the population were DMARD-treated at baseline

Reference	Reason for exclusion
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.
van Leeuwen 1993 ¹⁸⁵	No multivariate analysis

Reference	Reason for exclusion
van Nies 2015 ¹⁸⁷	Not adjusted for all key confounders.
van Steenberg 2015 ¹⁸⁸	Not adjusted for all key confounders.
van Steenberg 2015 ¹⁸⁹	Not adjusted for all key confounders.
van Tuyl 2010 ¹⁹⁰	Not adjusted for all key confounders.
van Zeven 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.2 Excluded health economic studies

Table 18: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.1 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	<ul style="list-style-type: none">• High: the research is essential to inform future updates of key recommendations in the guideline.