
Article:
Archer, R., Hock, E. orcid.org/0000-0002-8617-8875, Hamilton, J. orcid.org/0000-0003-3326-9842 et al. (6 more authors) (2018) Assessing prognosis and prediction of treatment response in early rheumatoid arthritis: systematic reviews. Health Technology Assessment, 22 (66). pp. 1-294. ISSN 1366-5278

https://doi.org/10.3310/hta22660

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 22 ISSUE 66 NOVEMBER 2018
ISSN 1366-5278

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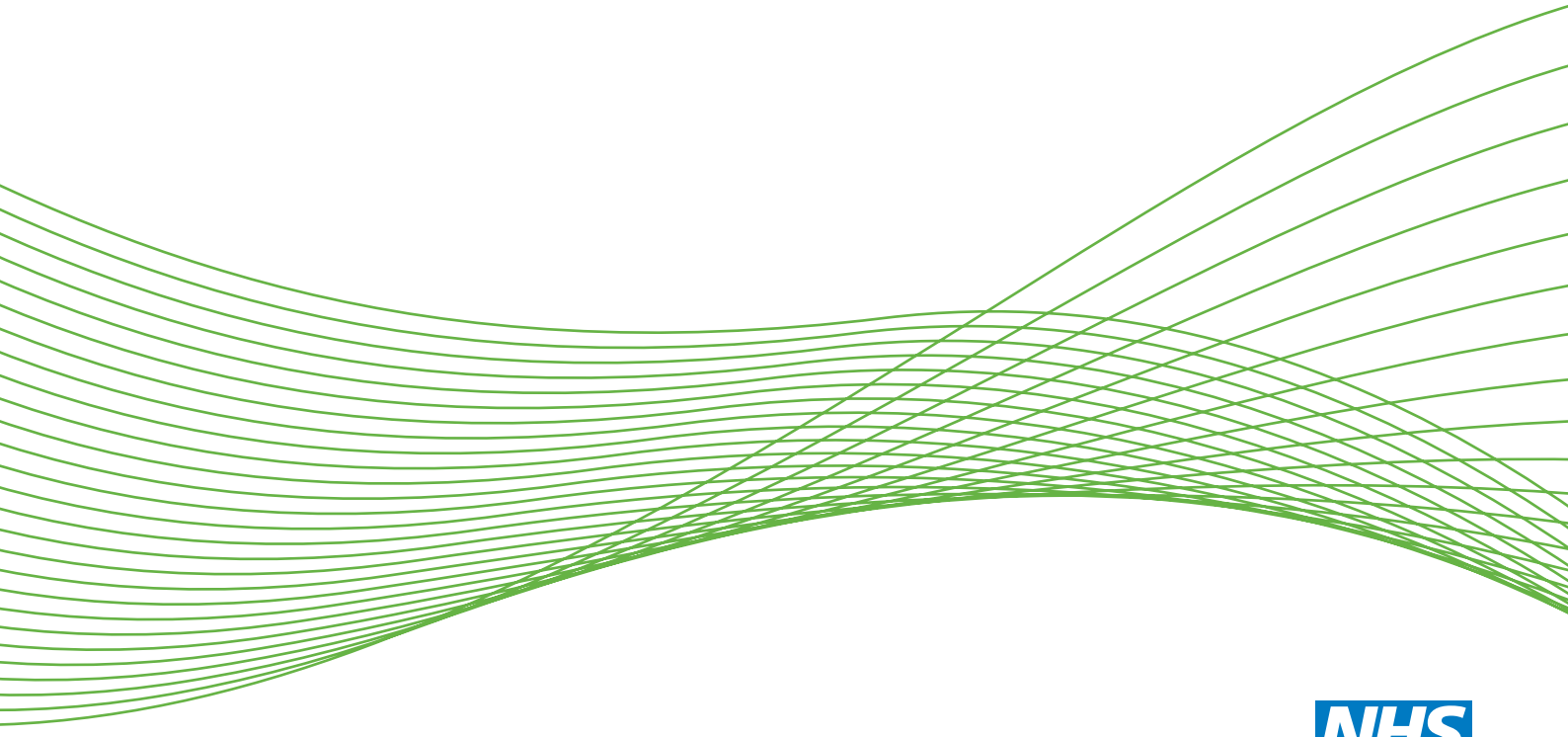

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DOI 10.3310/hta22660

Assessing prognosis and prediction of treatment response in early rheumatoid arthritis: systematic reviews

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Declared competing interests of authors: John Stevens is a shareholder of GlaxoSmithKline plc (GSK House, Middlesex, UK), AstraZeneca plc (Cambridge, UK) and Shire Pharmaceuticals Group plc (Shire plc, Dublin, Republic of Ireland).

Published November 2018
DOI: 10.3310/hta22660

This report should be referenced as follows:

Archer R, Hock E, Hamilton J, Stevens J, Essat M, Poku E, *et al*. Assessing prognosis and prediction of treatment response in early rheumatoid arthritis: systematic reviews. *Health Technol Assess* 2018;**22**(66).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 14/151/08. The contractual start date was in June 2016. The draft report began editorial review in August 2017 and was accepted for publication in February 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Assessing prognosis and prediction of treatment response in early rheumatoid arthritis: systematic reviews

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Background: Rheumatoid arthritis (RA) is a chronic, debilitating disease associated with reduced quality of life and substantial costs. It is unclear which tests and assessment tools allow the best assessment of prognosis in people with early RA and whether or not variables predict the response of patients to different drug treatments.

Objective: To systematically review evidence on the use of selected tests and assessment tools in patients with early RA (1) in the evaluation of a prognosis (review 1) and (2) as predictive markers of treatment response (review 2).

Data sources: Electronic databases (e.g. MEDLINE, EMBASE, The Cochrane Library, Web of Science Conference Proceedings; searched to September 2016), registers, key websites, hand-searching of reference lists of included studies and key systematic reviews and contact with experts.

Study selection: Review 1 – primary studies on the development, external validation and impact of clinical prediction models for selected outcomes in adult early RA patients. Review 2 – primary studies on the interaction between selected baseline covariates and treatment (conventional and biological disease-modifying antirheumatic drugs) on salient outcomes in adult early RA patients.

Results: Review 1 – 22 model development studies and one combined model development/external validation study reporting 39 clinical prediction models were included. Five external validation studies evaluating eight clinical prediction models for radiographic joint damage were also included. *c*-statistics from internal validation ranged from 0.63 to 0.87 for radiographic progression (different definitions, six studies) and 0.78 to 0.82 for the Health Assessment Questionnaire (HAQ). Predictive performance in external validations varied considerably. Three models [(1) Active controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset (ASPIRE) C-reactive protein (ASPIRE CRP), (2) ASPIRE erythrocyte sedimentation rate (ASPIRE ESR) and (3) Behandelings Strategie (BeSt)] were externally validated using the same outcome definition in more than one population. Results of the random-effects meta-analysis suggested substantial uncertainty in the expected predictive performance of models in a new sample of patients. Review 2 – 12 studies were identified. Covariates examined included anti-citrullinated protein/peptide anti-body (ACPA) status, smoking status, erosions, rheumatoid factor status, C-reactive protein level, erythrocyte sedimentation rate, swollen joint count (SJC), body mass index and vascularity of synovium on power Doppler ultrasound (PDUS). Outcomes examined included erosions/radiographic progression, disease activity, physical function and Disease Activity Score-28 remission. There was statistical evidence to suggest that ACPA status, SJC and PDUS status at baseline may be treatment effect modifiers, but not necessarily that they are prognostic of response for all treatments. Most of the results were subject to considerable uncertainty and were not statistically significant.

Limitations: The meta-analysis in review 1 was limited by the availability of only a small number of external validation studies. Studies rarely investigated the interaction between predictors and treatment.

Suggested research priorities: Collaborative research (including the use of individual participant data) is needed to further develop and externally validate the clinical prediction models. The clinical prediction models should be validated with respect to individual treatments. Future assessments of treatment by covariate interactions should follow good statistical practice.

Conclusions: Review 1 – uncertainty remains over the optimal prediction model(s) for use in clinical practice. Review 2 – in general, there was insufficient evidence that the effect of treatment depended on baseline characteristics.

Study registration: This study is registered as PROSPERO CRD42016042402.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Accuracy The degree to which a measurement or estimate agrees with the true value.

Apparent validation A form of internal validation using exactly the same population as that used for the model development.

Area under the curve An alternative term used to describe the *c*-statistic. In a logistic regression analysis, the *c*-statistic can be interpreted as the area under the receiver operating characteristic curve.

Calibration This describes the extent to which the expected outcomes (predicted by the model) and observed outcomes agree.

Clinical prediction model A formal combination of multiple predictors, from which the probability of occurrence of a specific clinical outcome can be estimated for individual patients. Commonly developed to aid health-care providers in their decision-making.

Correlation A measure of the statistical relationship, whether or not causal, between two random variables.

Cross-validation A statistical technique commonly used for the internal validation of a clinical prediction model, which aims to limit overfitting. As with data splitting, separate partitions of the data set are used for deriving the model and evaluating the model performance. Cross-validation extends the simple data-splitting approach by iterating the procedure over several partitions of the data set. The performance results are averaged to provide an overall measure.

Data splitting A statistical technique commonly used for the internal validation of a clinical prediction model, which aims to limit overfitting. Data are divided into a training data set (used to derive the model) and a validation data set that is used to evaluate the model's performance.

Discrimination Describes the ability of the clinical prediction model to distinguish between individuals who do and do not experience the outcome of interest.

Effect modifier A covariate that alters the relative effect of treatments on outcomes, so that the treatment is more or less effective in different subgroups formed by levels of the effect modifier. Effect modifiers are not necessarily also prognostic variables. The effect modifier status is specific to a given scale: the positive status of a covariate as an effect modifier on one scale does not necessarily imply, either positively or negatively, an effect modifier status on another scale; however, a covariate that is not an effect modifier on one scale is guaranteed to be an effect modifier on another.

External validation This is used to quantify the performance of a clinical prediction model in a population that is external to that which was used for the model development.

Interaction An interaction arises between two or more variables when their joint impact on a dependent variable is greater than the sum of their individual contributions.

Internal validation Used to quantify the performance of a clinical prediction model in the population used to develop the model.

Logistic regression A statistical technique used to model the relationship between a binary outcome variable and one or more covariates of interest.

Main effect The effect of an independent variable on a dependent variable averaging across the levels of any other independent variables.

Meta-analysis A statistical method by which the results of a number of studies are aggregated to provide a combined summary statistic.

Negative predictive value For individuals who are not expected to experience the outcome of interest (as predicted by the model), the proportion who do not experience the outcome.

Overfitting Occurs when a model is optimally designed to fit the development data set and performs less favourably in more general situations.

Positive predictive value For individuals who are expected to experience the outcome of interest (as predicted by the model), the proportion who experience the outcome.

Prognostic variable A covariate that affects (or is prognostic of) the outcome. We make the distinction between prognostic variables and effect modifiers; effect modifiers are not necessarily also prognostic variables.

R^2 A measurement of overall model performance that describes the proportion of explained variation.

Sensitivity For individuals who are known to experience the outcome of interest, the proportion that were correctly predicted (using the clinical prediction model) to experience the outcome.

Shrinkage A statistical estimation procedure that preshrinks regression coefficients towards zero, so that the clinical prediction model will not need to be recalibrated in a new data set. Also linked to the shrinkage factor of a calibration plot, which will be less than one when a clinical prediction model is applied to a new data set, if overfitting has occurred during the model development.

Specificity For individuals who are known not to experience the outcome of interest, this is the proportion that was correctly predicted (using the clinical prediction model) not to experience the outcome.

List of abbreviations

ABT	abatacept
ACPA	anticitrullinated protein/peptide anti-body
ACR	American College of Rheumatology
ADA	adalimumab
ADL	Activities of Daily Living
AhFibA	anti-human citrullinated fibrinogen anti-body
ANOVA	analysis of variance
anti-CCP	anticyclic citrullinated peptide
anti-MCV	antimutated citrullinated vimentin
ASPIRE	Active controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset
ATTRACT	anti-TNF trial in rheumatoid arthritis with concomitant therapy
AUC	area under the curve
bDMARD	biologic disease-modifying antirheumatic drug
BeSt	Behandel Strategieen
BMI	body mass index
cDMARD	conventional disease-modifying antirheumatic drug
CG79	Clinical Guidance number 79
CHARMS	CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
CI	confidence interval
CRP	C-reactive protein
CsA	ciclosporin A
DARE	Database of Abstracts of Reviews of Effects
DAS	Disease Activity Score
DAS28	Disease Activity Score-28
DMARD	disease-modifying antirheumatic drug
ERO	erosive
ESPOIR	Étude et suivi des polyarthrites indifférenciées récentes
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European League Against Rheumatism
FE	fixed effects
GSTM	gold sodium thiomalate
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – disability index
HCQ	hydroxychloroquine
HLA	human leucocyte antigen
HTA	Health Technology Assessment
IFX	infliximab
IMPROVED	Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritis Disease
IPD	individual participant data
IQR	interquartile range
LEF	leflunomide
MBDA	multibiomarker disease activity
MHAQ	modified Health Assessment Questionnaire
MMP	matrix metalloproteinase
MTX	methotrexate
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
O : E	observed to expected (ratio)
OR	odds ratio

PDUS	power Doppler ultrasound
PPV	positive predictive value
PR	predicted risk
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBAST	Prediction model study Risk Of Bias Assessment Tool
PROGRESS	PROGnosis RESearch Strategy
QUIPS	Quality in Prognosis Studies
RA	rheumatoid arthritis
RCT	randomised controlled trial
RE	random effects
RF	rheumatoid factor
RRP	rapid radiographic progression
ScHARR	School of Health and Related Research
SD	standard deviation
SE	shared epitope
SHS	Sharp–van der Heijde score
SJC	swollen joint count
SJC28	28 swollen joint count
SONORA	Study Of New-Onset Rheumatoid Arthritis
SSZ	sulfasalazine
SWEFOT	Swedish Farmacotherapy
TAR	Technology Assessment Review
TNF	tumour necrosis factor
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
TSS	total Sharp score
TTT	treat to target

Plain English summary

Rheumatoid arthritis (RA) is a chronic disease that can cause disability and pain. Health professionals need to be able to judge at an early stage of disease which patients may experience more severe RA or respond better to different treatments. This assessment aimed to (1) study tools that identify, at an early stage of disease, the disease course and (2) determine whether or not there are any patient characteristics that predict which patients are likely to respond best to particular treatments.

Twenty-three studies were found that tried to predict the severity of disease using patient characteristics. Six studies assessed how well these predictions performed in different groups of patients. Results were mixed, showing that a tool that performs well for one group of patients may not perform well for others. Further research is needed to understand which combinations of patient characteristics best predict the severity of disease in patients with early RA.

Twelve studies were found that allowed us to find out whether or not different patient characteristics can predict different treatment effects. Ten characteristics were assessed. The results were inconclusive, although the benefit of some treatments seemed to differ according to different patient characteristics. Further research is needed to understand how treatment benefit varies by patient characteristics.

Scientific summary

Background

Rheumatoid arthritis (RA) is a chronic and debilitating disease that can lead to increasing disability, pain and irreversible joint damage. Symptoms include pain, morning stiffness, swelling and tenderness of joints, loss of mobility, warmth of the peripheral joints and fatigue. RA is associated with a reduced quality of life and substantial direct and indirect costs resulting from treatment and reductions in productivity. Treatments for RA include conventional disease-modifying antirheumatic drugs (cDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs). Key outcomes in RA include measures of joint destruction (e.g. radiographic progression), disease activity [as assessed via, for example, the Disease Activity Score-28 (DAS28)] and disability [as assessed via, for example, the Health Assessment Questionnaire (HAQ) scores].

Health-care professionals need to be able to determine at an early stage of disease which patients may experience a worse prognosis in order to inform effective disease management and avoid pharmacological overtreatment of patients. There is currently no clear consensus on which of the available tests and assessment tools used in RA provide the best assessment of prognosis in people newly diagnosed with RA and whether or not patient or disease characteristics can predict how well patients will respond to different drug treatments.

This report was commissioned by the National Institute for Health Research Health Technology Assessment programme as project number 14/151/08.

Objectives

The objectives of this work were to undertake systematic reviews to determine the:

- use of selected tests and assessment tools in the evaluation of prognosis in patients with early RA
- potential of selected tests and assessment tools as predictive markers of treatment response in patients with early RA.

Methods

Two related systematic reviews were undertaken. The systematic reviews were informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.prisma-statement.org/) and current good practice in prognostic reviews advocated by the Cochrane Prognosis Methods Group (http://methods.cochrane.org/prognosis/). A final protocol for this assessment was registered on PROSPERO (CRD42016042402).

Review 1 (clinical prediction models)

Prognostic research involves the study of the relationship between future outcomes among people with a given baseline health state in order to improve health. A prognostic model is a formal combination of multiple predictors from which the probability of a specific event can be estimated for individual patients.

Searches of electronic databases (e.g. MEDLINE, EMBASE, The Cochrane Library, Web of Science Conference Proceedings; searched to September 2016), registers, relevant websites, hand-searching of reference lists of included studies and key systematic reviews were conducted and contact was made with experts.

Primary studies describing the development, external validation and impact of eligible clinical prediction models in adult patients with early RA (defined as being within 2 years of the onset of symptoms) were eligible for inclusion. The prognostic variables considered in the assessment were informed by the phase 1 scoping searches and agreed following discussion between the review team and clinical advisors. The prognostic variables selected for inclusion in review 1 were anticitrullinated protein/peptide anti-bodies (ACPAs), rheumatoid factor, erosions/joint damage assessed via X-ray, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), swollen joint count (SJC), DAS28, early RA untreated for $\geq$ 12 weeks following the onset of symptoms, smoking status and HAQ scores. Eligible outcomes were joint damage as assessed on radiographs, DAS28 and HAQ scores.

Data extraction was informed by the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS). Assessment of the study quality characteristics of clinical prediction modelling studies was informed by criteria included in the Prediction model study Risk Of Bias Assessment Tool (PROBAST).

Data on the predictive performance of included clinical prediction models were described in a narrative synthesis, presented separately for internal and external validation studies. Evidence synthesis using meta-analysis was considered for external validation studies.

Review 2 (prediction of treatment response)

Searches for evidence were undertaken using data sources, as described for review 1.

Review 2 included evidence on the interaction between baseline covariates and treatment on salient outcomes in adult patients with early RA. The response to cDMARDs and bDMARDs was studied. Eligible studies involved at least 6 months' treatment duration (with the exception of 12 weeks for certolizumab pegol). Eligible predictive variables were the same as for review 1, with the addition of body mass index (BMI) and vascularity of synovium assessed using power Doppler ultrasound (PDUS). The outcomes selected for inclusion were the same as for review 1, with the addition of selected definitions of response/remission [European League Against Rheumatism (EULAR) response; remission as a DAS28 of $<$ 2.6, a Disease Activity Score of $<$ 1.6 and/or American College of Rheumatology/EULAR remission].

Studies of predictive variables were assessed by criteria informed by the Quality in Prognosis Studies (QUIPS) tool.

A formal meta-analysis was not performed as, for specific outcome measures and potential treatment effect modifiers, there were no studies that shared any treatments in common. Results were presented with regard to assessing the predictive ability of baseline patient and/or disease characteristics according to different treatments by study.

Results

Review 1 (clinical prediction models)

Twenty-eight studies that investigated the use of assessment tools and tests in the evaluation of a prognosis in early RA patients were identified. These included 22 model development studies and one combined model development/external validation study that reported a total of 39 clinical prediction models for the outcomes of radiographic joint damage, DAS28 and HAQ score. An additional five external validation studies, which tested the performance of eight clinical prediction models for radiographic joint damage outcomes, were also included.

Included studies varied in terms of the methods applied to develop the clinical prediction models, for example, in the strategies used to select or reject candidate predictors from the final model and in the handling of continuous predictors. Several studies presented a 'matrix model', and continuous variables

were frequently categorised to allow this presentation format. For models developed using randomised controlled trial data with patients assigned to alternative treatment strategies, the model development generally failed to assess interactions between predictors and treatment group and so did not generate truly treatment-specific models.

Model development studies varied in the reporting of predictive performance. A key measure of model predictive performance, the *c*-statistic, was presented from internal validation in 8 of the 23 model development studies; sensitivity and specificity (eight studies), accuracy (seven studies), positive predictive value and/or negative predictive value (12 studies) were also reported. Of the eight studies that reported *c*-statistics from internal validations, *c*-statistics for radiographic progression outcomes ranged between 0.63 [with Degboé *et al.* (Degboé Y, Constantin A, Nigon D, Tobon G, Cornillet M, Schaeverbeke T, *et al.* Predictive value of autoantibodies from anti-CCP2, anti-MCV and anti-human citrullinated fibrinogen tests, in early rheumatoid arthritis patients with rapid radiographic progression at 1 year: results from the ESPOIR cohort. *RMD Open* 2015;**1**:e000180) predicting a Δ Sharp/van der Heijde score (SHS) of ≥ 5 at 1 year] and 0.87 [with Houseman *et al.* (Houseman M, Potter C, Marshall N, Lakey R, Cawston T, Griffiths I, *et al.* Baseline serum MMP-3 levels in patients with rheumatoid arthritis are still independently predictive of radiographic progression in a longitudinal observational cohort at 8 years follow up. *Arthritis Res Ther* 2012;**14**:R30) predicting a Δ SHS of ≥ 10.5 at 8.2 years]. Two studies predicting HAQ also generated *c*-statistics from internal validation {0.78 [Dirven *et al.* (Dirven L, Visser K, Klarenbeek NB, Ewals JA, Han KH, Peeters AJ, *et al.* Towards personalized treatment: predictors of short-term HAQ response in recent-onset active rheumatoid arthritis are different from predictors of rapid radiological progression. *Scand J Rheumatol* 2012;**41**:15–19) HAQ ≥ 1 at 3 months] to 0.82 [Bansback *et al.* (Bansback N, Young A, Brennan A, Dixey J. A prognostic model for functional outcome in early rheumatoid arthritis. *J Rheumatol* 2006;**33**:1503–10) HAQ ≥ 1.5 at 5 years]}. However, even if consistent approaches had been used for internal validation, comparing the performance of clinical prediction models that have been internally validated in different populations would still be limited, because good discriminative ability in the population used to develop the model would be expected. External validation is required to provide an objective comparison.

For the eight models that were externally validated, predictive performance varied considerably. Five clinical prediction models [Syversen, Swedish Farmacotherapy (SWEFOT), Étude et suivi des polyarthrites indifférenciées récentes (ESPOIR), multibiomarker disease activity and Study Of New-Onset Rheumatoid Arthritis (SONORA)] were externally validated only in one population per outcome definition. Three clinical prediction models [Active controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset (ASPIRE) CRP, ASPIRE ESR and Behandelings Strategie (BeSt)] were externally validated using the same outcome definition in more than one population. The results of the random-effects meta-analysis indicated that the most favourable performance across external validations was for the BeSt model [*c*-statistic 0.72, 95% confidence interval (CI) 0.20 to 0.96], followed by ASPIRE ESR (*c*-statistic 0.62, 95% CI 0.44 to 0.78) and ASPIRE CRP (*c*-statistic 0.55, 95% CI 0.13 to 0.91). However, there is considerable heterogeneity for all three models, with the wide CIs suggesting substantial uncertainty in the expected predictive performance in a new sample of patients. The 95% CIs of the pooled estimates contain 0.5 for all three clinical prediction models, indicating that there is limited confidence that the performance of the models is better than would be expected by chance.

The inconsistent results generated by the clinical prediction models on external validation indicate that there is heterogeneity in the populations in which the models are being tested that is not explained by the currently proposed models. However, the meta-analysis was limited by the small number of available external validation studies. The synthesised estimates are indicative of performance in the observed studies, but cannot be used to provide a definitive conclusion about the performance in future studies or to explore the reasons for the heterogeneity between studies.

Despite the identification of 23 model development studies and six external validations (including the combined model development/external validation study), uncertainty remains over the optimal prediction model(s) for use in clinical practice. There were limitations identified in the methods used to develop the

clinical prediction models in many of the development studies, including the handling of continuous predictors and failure to assess interactions. It is therefore likely that the most clinically useful prediction model may contain predictors from across more than one of the reviewed clinical prediction models and/or consider alternative handling of key predictive variables.

Review 2 (prediction of treatment response)

Review 2 identified 12 primary studies with which to assess the prediction of treatment response according to baseline covariates. The covariates examined included ACPA status, smoking status, erosions, rheumatoid factor status, CRP levels, ESR, SJC, BMI and vascularity of synovium on PDUS. The outcomes examined included erosions/radiographic progression, disease activity, physical function and DAS28 remission.

There was statistical evidence to suggest that ACPA status, SJC 28 and PDUS status at baseline may be treatment effect modifiers, but not necessarily that they are prognostic of response for all treatments. Most of the results were subject to considerable uncertainty and were not statistically significant. In general, there was insufficient evidence that the effect of treatment depended on baseline characteristics.

Conclusions

Review 1 (prognostic models)

No single clinical prediction model can currently be recommended in preference to any other for use in clinical practice on the basis of uncertainties and limitations in the available evidence. The optimal prediction model(s) may include variables (e.g. biomarkers/genetic tests) that are not routinely or currently available. Any practical and cost implications associated with their use would need to be evaluated before future implementation.

Review 2 (prediction of treatment response)

There was limited evidence with which to assess whether or not specific baseline variables can predict differential effects according to the treatment administered. Nevertheless, the available evidence suggested that some baseline variables do affect relative treatment effects and that not all baseline variables may be prognostic of response for all treatments.

The effects of covariates were rarely assessed in single models adjusting for all covariates and with the inclusion of interaction terms with treatment. Although there was statistical evidence to suggest that some baseline covariates affect treatment response differentially, the results were subject to considerable uncertainty and there was generally insufficient evidence that the effect of treatment depended on baseline characteristics. This may be a real effect or may be because studies lacked statistical power to detect interaction effects. In future analyses, the true effect of baseline variables should be evaluated in single multivariable models, adjusting for all relevant covariates and interactions with treatment.

Suggested research priorities

Review 1 (prognostic models)

Recommendations for further research include:

- collaborative research, including the use of individual participant data, for further (1) development/internal validation and (2) external validation of optimal clinical prediction model(s) to demonstrate predictive performance and generalisability
- adherence to good model development and reporting standards of future clinical prediction model studies
- research to investigate the effects on patient outcomes (and the cost-effectiveness) of the use in clinical practice of optimal internally and externally validated model(s).

Review 2 (prediction of treatment response)

Recommendations for further research include the following:

- Clinical prediction models should be developed and validated with respect to individual treatments.
- The assessment of treatment by covariate interactions should follow good statistical practice: subgroup analyses should be avoided, categorising continuous baseline covariates should be avoided and the interactions between treatments and baseline variables should be specifically modelled.
- The results of multivariable analyses presented in published reports should include estimates of the main effects of covariates and any interaction effects together with their standard errors and covariances for secondary research purposes.

Study registration

This study is registered as PROSPERO CRD42016042402.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the health problem

Clinical features of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic disease characterised by progressive, irreversible joint damage, impaired joint function, pain, swelling and tenderness of joints.[1] RA is associated with increasing disability and reduced quality of life.[1] Symptoms of RA include pain, morning stiffness, joint swelling, joint tenderness, loss of movement, warmth of the peripheral joints and fatigue.[2,3] RA is associated with substantial costs, both directly (in terms of drug acquisition and hospitalisation) and indirectly, because of reduced productivity.[4] RA has long been linked with increased mortality,[5,6] in particular because of cardiovascular events.[7]

Epidemiology

It has been estimated that there are approximately 400,000 people in the UK with RA.[8] RA has been reported to have a greater incidence in females (3.6 per 100,000 per year) than in males (1.5 per 100,000 per year).[9] Although the peak age of incidence in the UK is in the eighth decade of life, people of all ages may develop RA.[9]

Aetiology

A range of contributing factors, such as genetic and environmental influences, have been implicated as potential causes of RA. The heritability of RA is estimated to be between 53% and 65%,[10] with a family history of RA carrying a corresponding risk ratio of 1.6 compared with the general population.[11] Many genes linked with RA susceptibility are concerned with immune regulation. Although infectious agents have been suspected, no consistent relationship with an infective agent has been demonstrated. Sex hormones have also been implicated because of the higher prevalence of RA in women and a tendency for RA to improve during pregnancy. There is no proof of any causal link with lifestyle factors, such as diet, smoking or occupation (but lifestyle factors may increase the risk of developing RA).

Management of rheumatoid arthritis

There are a range of treatment options available for the management of RA, with the aim of alleviating symptoms and of minimising irreversible joint damage that may occur as a result of the disease process.[8]

Traditionally, patients have been treated with conventional disease-modifying antirheumatic drugs [(cDMARDs) also known as conventional synthetic disease-modifying antirheumatic drugs], including methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF) and gold injections, as well as corticosteroids, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). However, more recently, a group of biologic immunosuppressant drugs have been developed that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes).[8] These treatments have been termed as biologic disease-modifying antirheumatic drugs (bDMARDs); of these, certolizumab pegol, adalimumab (ADA), etanercept (ETN), golimumab and infliximab (IFX) are tumour necrosis factor (TNF) inhibitors (or antagonists). Of the remaining bDMARDs, tocilizumab is a cytokine interleukin-6 inhibitor, abatacept (ABT) is a selective modulator of the T-lymphocyte activation pathway and rituximab is a monoclonal anti-body against the cluster of differentiation 20 (CD20) protein. For patients who have exhausted all National Institute for Health and Care Excellence (NICE)-recommended treatments, non-biologic final treatment options may be used.

Prompt diagnosis of RA is important in ensuring the appropriate clinical management of patients early in the course of the disease. The 2013 European League Against Rheumatism (EULAR) recommendations for the management of RA state that treatment with disease-modifying antirheumatic drugs (DMARDs) should begin as soon as RA is diagnosed.[12] The lack of sensitivity of the 1987 American College of

Rheumatology [(ACR) previously known as the American Rheumatism Association] classification criteria in early disease has been acknowledged and led to the development of the 2010 RA classification criteria.[13] The 2010 criteria for RA require (for classification as definite RA) the confirmed presence of synovitis in at least one joint, the absence of an alternative diagnosis to better explain the synovitis and scoring ≥ 6 (of a maximum of 10) from individual scores across four domains: (1) number and site of affected joints (score range 0–5), (2) serological abnormality (score range 0–3), (3) elevated acute-phase response (score range 0–1) and (4) symptom duration (range 0–1).[13]

The EULAR recommended that, if a treatment target is not reached, the use of a bDMARD should be considered in the presence of poor prognostic factors [e.g. high disease activity, positivity to rheumatoid factor (RF) and/or anti-bodies to citrullinated proteins and the early presence of joint damage].[14]

Rheumatoid arthritis is a heterogeneous disease and the disease course can vary considerably between patients. The guideline development group for the NICE guidance on RA [i.e. Clinical Guidance number 79 (CG79)] suggested that it would be useful to clinicians if they could identify at an early stage those RA patients who are most likely to suffer a worse course of disease (or prognosis).[8] These patients could then be closely monitored to ensure that they can receive appropriate treatment to minimise the health problems and joint damage caused by RA. Patients who are considered to be less likely to experience a poor prognosis may require a less intensive follow-up and treatment strategy. The provision of clearer information on the prognosis and prediction of treatment response would be useful to inform the optimal clinical management of patients and to avoid pharmacological overtreatment of patients.

The NICE guidance on RA (i.e. CG79) indicated the potential role of a range of factors in determining the prognosis of patients with early RA.[8] These included RF, anticyclic citrullinated peptide (anti-CCP) positivity, baseline radiological damage, nodules, acute-phase markers, Health Assessment Questionnaire (HAQ) score, grip strength and swollen joint counts (SJCs).

Although there is a large amount of evidence available on the use of tests and assessment tools in determining the prognosis and prediction of treatment response, a recent good-quality evidence synthesis was considered to be lacking. Therefore, there is no clear consensus on which of the available tests and assessment tools used for RA could allow the best assessment of prognosis in people newly diagnosed with RA and whether or not variables, if identified, also predict how well patients respond to different drug treatments.

Measurement of key outcomes in rheumatoid arthritis

Major outcomes in RA include measures of joint destruction (e.g. radiographic progression), disease activity [as assessed via, for example, Disease Activity Score-28 (DAS28)] and disability (as assessed via, for example, HAQ scores).

Radiographic progression is frequently measured in clinical trials and observational research.[15] The two main scoring systems available for measuring radiographic progression are the Larsen *et al.*[16] system and the Sharp *et al.*[17] system. The van der Heijde[18] modification of the Sharp system includes both hands and feet, erosions, joint-space narrowing and a range of joints.

In the UK, monitoring the progression of RA is often undertaken using the DAS28 in terms of swelling (SW28) and of tenderness to the touch (TEN28). The DAS28 also incorporates erythrocyte sedimentation rate (ESR) and a subjective assessment on a scale of 0–100 made by the patient regarding disease activity in the previous week.

The equation for calculating DAS28 is as follows:[19]

$$\text{DAS28} = 0.56 \times \text{TEN28}^{0.5} + 28 \times \text{SW28}^{0.5} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{subjective assessment}. \quad (1)$$

A second version of the DAS28 using C-reactive protein (CRP) levels instead of ESR exists. The DAS28 can be used to classify both the disease activity of the patient and the level of improvement. Patients with a DAS28 of ≤ 3.2 are classed as having inactive disease, patients with a DAS28 of > 3.2 and ≤ 5.1 are regarded as having moderate disease and those with a DAS28 of > 5.1 are regarded as having very active disease.[19]

The HAQ is a key measure of patient functional disability.[20] It is a patient-completed assessment resulting in scores ranging from 0 to 3 (with higher scores indicating greater disability).

Background to prognosis research

Key concepts in prognosis research

Prognosis research describes the investigation of the relationship between future outcomes among people with a given baseline health state in order to improve health.[21,22]

The PROGnosis RESearch Strategy (PROGRESS) partnership outlined a framework for prognostic research, with the aim of enhancing the quality and translational impact of prognosis research findings. The framework has four key elements, as outlined below:

1. Fundamental prognosis research – examining the average prognosis of patients (natural course of a disease or condition) with current clinical practice.[21,22]
2. Prognostic factor research – studying individual factors that, for patients with a given disease or condition, are associated with the clinical outcome of interest.[21,22]
3. Prognostic model research – the use of multiple prognostic factors in combination to provide a clinical prediction model, from which the probability of the outcome can be predicted for individuals. This research theme includes model development, validation and assessing the clinical impact of these models.[23]
4. Stratified medicine research – the use of prognostic information to predict an individual's response to treatment, and hence make treatment decisions that are tailored to individuals.[24]

The current assessment focuses on prognostic model research (theme 3) and stratified medicine (theme 4). Briefly, prognostic model research seeks to estimate the absolute response of an outcome for an individual, whereas stratified medicine seeks to target therapy and make the best decisions for groups of similar patients.[23] One approach to stratifying the use of treatments is to consider the absolute response of each individual (as estimated using a prognostic model). Those people with the most severe prognosis are likely to derive the largest absolute benefit from a treatment and may be targeted for intervention. For example, lipid-lowering therapy may be recommended to individuals above a certain threshold for the risk of developing cardiovascular disease.[25] The results from prognostic model research are therefore relevant for guiding stratified medicine research, and the two themes are related.

Clinicians may also stratify medicine because the relative treatment effect is inconsistent across patients. In statistical terms, this means that the patient or disease characteristic is a treatment effect modifier (i.e. there is an interaction between the patient or disease characteristic and the effect of treatment on the outcome). Assessing the presence of these differential treatment effects is important in predicting individual treatment response. Examples include the use of trastuzumab for the treatment of breast cancer in individuals with a positive human epidermal growth factor receptor-2 status. The prediction of treatment response is considered in review 2, and further background on the development of treatment-specific clinical prediction models is given in *Background to stratified medicine research*. Further examples of stratified treatment decisions in clinical practice, based on the prediction of absolute risks, or differential treatment effects across different subgroups of the population are provided by Hingorani *et al*.[24]

Definition of a prognostic model

Prognostic models are developed to aid health-care providers in their decision-making by estimating the probability that a specific event will occur in the future.[23,26]

Moons *et al.*[27] stated that, because of the complexities in patients and diseases, prognostic studies require a multivariable approach. Indeed, Collins *et al.*[26] noted that, in practice, the prediction of an individual's response is not typically based on a single predictor and that clinicians integrate a range of patient characteristics and symptoms in their own estimation of prognosis.[26] We further acknowledge that clinical prediction models would simplify to only one variable if this were the only significant predictor of prognosis.

A prognostic model is a formal combination of multiple predictors from which the probability of a specific outcome can be estimated for individual patients.[23,27] For an individual with a given set of baseline characteristics and assuming that the outcome is binary (e.g. progression/no progression), a prognostic model provides an estimate of the probability of experiencing the outcome within a specific period of time (i.e. an estimate of absolute risk). Measures of relative risk [e.g. odds ratios (ORs), relative risks, hazard ratios] are not relevant when evaluating the performance of prognostic models, other than to obtain an estimate of the absolute risk in conjunction with a baseline response.[28]

Clinical prediction model development

Prediction model studies may be classed as model development,[29] model validation[30] or comprise a combination of both. There are many important statistical considerations to the development process, which we summarise here briefly to aid interpretation of the results. More comprehensive descriptions of model development and validation procedures are given in the provided references.

Clinical prediction models are developed using data from cohorts of patients or clinical trials. The development procedure starts with a preselected set of candidate predictors, and suitable procedures should be used to identify the most important predictors and assign relative weights to the predictors to form the combined clinical prediction model.[31] Important considerations include the following:

- The selection of candidate predictors. Candidate predictors are variables that are chosen to be studied for their prognostic performance.[31] They should be selected based on subject knowledge and availability in practice, with consideration to the size of the data set.[32] Selection based on univariable analyses could lead to the omission of important predictors and so should be avoided.[33]
- The handling of missing values. It is generally recommended that some form of imputation should be used to account for missing data, because an analysis including only the individuals with completely observed data may lead to biased results.[34] A complete-case analysis may be appropriate, provided that the proportion of missing values is small (i.e. typically $< 5\%$).[33]
- Continuous predictors. Simple transformations of continuous variables to account for non-linearity may be appropriate.[31] The creation of artificial categories leads to a loss of information and power and should therefore be avoided.[35,36]
- Final variable selection. Clinical prediction models are usually developed using multivariable regression. If a full-model approach (containing all candidate variables) is not appropriate, then backwards selection is the preferred method for statistical selection. Selection based purely on statistical significance in univariable analysis should not be used.[31,37,38]
- Interactions between variables should also be considered. Interactions between variables and treatment (treatment effect modification) are considered in review 2.

After a model has been developed, validation is conducted to quantify the performance of the model in the population used to develop the model (internal validation). This is described as *apparent validation* if the validation is conducted in exactly the same sample as that used for model development. This usually produces the best-possible estimate of model performance, because the model was optimally designed to fit the development data set (described as *overfitting*) and performs less favourably when applied generally to similar samples of patients.[31] Overfitting is of particular concern when the development data set is small and/or the number of candidate predictors is high.[31]

Alternatives to apparent validation should ideally be used. *Data splitting* involves dividing the development sample into a training data set (used to derive the model) and a validation data set that is used to evaluate model performance. However, this approach is considered to be statistically inefficient, as not all available data are used to formulate the model.[31] Therefore, either *bootstrapping* or *cross-validation* is recommended as the preferred method of internal validation.[26] Cross-validation extends the simple data-splitting approach by iterating the procedure over several partitions of the data set. The performance results are averaged to provide an overall measure.

Overfitting can also be avoided or minimised using a procedure called *shrinkage*. This is a statistical estimation method that preshrinks the model regression coefficients towards zero.[33]

Measures of predictive model performance (binary outcomes)

There are several summary measures used to quantify the predictive performance of clinical prediction models in internal and external validation. The following key measures of predictive model performance are considered in the assessment.

Overall model performance statistics

Overall model performance statistics include R^2 and the mean-squared error/Brier score. R^2 ranges from zero to one and describes the proportion of explained variation in the data. There are several methods for calculating R^2, with Nagelkerke's[39] R^2 commonly being reported for logistic regression models. The mean-squared error is defined as the average-squared difference between the observed outcome (0 or 1) and the predicted probability of the outcome.

Calibration

Calibration indicates the extent to which expected outcomes (predicted from the clinical prediction model) and observed outcomes agree. Summarising the estimates of calibration performance is challenging, because studies may quantify calibration using different summary statistics.[40] In a recently published guide to systematic review and meta-analysis of prediction model performance, Debray *et al.*[40] based their assessment of calibration on the total number of observed (O) events compared with the expected number of events (E) predicted by the model. The observed-to-expected (O : E) ratio provides a rough indication of the overall model calibration across the entire range of predicted probabilities. An O : E ratio of close to one would indicate good calibration, whereas values that are < 1 or > 1 indicate a model that either overestimates or underestimates the number of events.

Discrimination

Discrimination refers to the ability of a prediction model to distinguish between patients who do and those who do not experience the outcome of interest. For binary outcomes, discrimination is frequently quantified using the concordance statistic (*c*-statistic), and it is also known as the area under the receiver operating characteristic curve. For categorical outcomes, Harrell's *c*-statistic for ordinal data[37] can be used. The *c*-statistic is also relevant for other outcome measures (e.g. time to event) and is sometimes termed the *c*-index. A *c*-statistic of 0.5 indicates no discriminative ability over that that would be expected because of chance, whereas a *c*-statistic of 1 indicates perfect discriminative ability.

External validation

Demonstrating that a clinical prediction model can successfully predict the outcome of interest in the sample used to derive the model is not, by itself, sufficient to confirm its value.[23,28] A more objective measure of model performance is obtained using external validation, in which the model performance is assessed in a sample of patients who are external to those who were used for the model development.

Model updating or recalibration can be considered if a particular model does not calibrate well in external populations. This is considered to be a better alternative to redeveloping new models in each patient sample as a result of poor performance of existing models.[31] Despite this recommendation, a recent systematic review shows that recalibration is not commonly undertaken.[41]

The *c*-statistic of a clinical prediction model may vary substantially between different validation studies, and a common cause for this heterogeneity is because of differences in the distribution of patient characteristcs.[40] Vergouwe *et al.*[42] demonstrated in a simulation study that a more heterogeneous sample was related to a higher discriminative ability. It is therefore important to consider the distribution of patient characteristics (case mix) of the included validation studies. This could be done by considering the standard deviation (SD) of key variables or of the combined linear predictor (the weighted sum of regression weights and covariate values in the validation sample).

Background to stratified medicine research

Developing treatment-specific clinical prediction models

Stratified medicine research is concerned with the use of prognostic information to predict an individual's response (i.e. clinical benefit or adverse events) according to different treatments. The prediction of absolute treatment effects according to different patient and/or disease characteristics for different treatments is based on an analysis of relative treatment effects. The development of treatment-specific clinical prediction models should follow the same process as described in *Clinical prediction model development*; an assessment of differential treatment effects should be conducted formally, including the use of interaction tests, and not through subgroup analyses.

Issues associated with subgroup analyses

Although it is common for an assessment of differential treatment effects to be based on a series of subgroup analyses, this is not generally recommended. Constructing subgroups based on patient and/or disease characteristics that are continuous (e.g. ESRs of < 25 mm/hour, 25–50 mm/hour and > 50 mm/hour) assumes that treatment effects are constant within categories and have a discontinuity according to each category; in practice, such categorisation is often subjective and not supported by evidence. Some subgroups, including definitions such as early disease, involve other patient and/or disease characteristics that are correlated with such definitions of subgroup, and the resulting estimates of treatment effects may have a more complex interpretation. Absence of evidence is not evidence of absence, and a statistically significant treatment effect in one subgroup but not in another should not be interpreted as there being a true effect in one subgroup but not in another; the result may reflect different degrees of uncertainty or different magnitudes of treatment effect in the subgroups. Assessing the statistical significance of treatment effects in different subgroups does not incorporate an adjustment for other covariates that may be important and assumes that there is no residual differential treatment effect within the subgroup. Treatment effects may be misleading when treatments interact with covariates that were not used to form subgroups, and when the subgrouping variable interacts with a patient and/or disease characteristic that was ignored.[43]

Assessing treatment by covariate interactions

Ideally, patient and/or disease characteristics that may affect relative treatment effects should be prespecified. All covariates believed to be prognostic or treatment effect modifiers should be included in the analysis and should be used consistently across data sets irrespective of the statistical significance of the covariates. The main effects should be modelled flexibly and should not assume linearity of response with a change in the value of a covariate; interaction effects should be modelled using the same approach. The statistical significance of all interaction effects included in a model should be assessed using a single test; this controls for multiplicity and will not be affected by potential treatment effect modifiers that are colinear with each other. The absence of a statistically significant interaction effect should not necessarily be interpreted to mean that this is evidence of the absence of an interaction effect. Studies are not typically designed to assess interaction effects, and a lack of statistical significance may simply reflect a lack of power of the test. Similarly, some interaction tests may be statistically significant by chance. Furthermore, it is important when interpreting interaction effects to distinguish between qualitative interactions, whereby the effect of treatment is reversed for some value(s) of the covariate, and quantitative interactions, whereby the treatment effect is in the same direction for different values of the covariate, but the magnitude of the treatment effect is different and may be clinically irrelevant. Finally, in non-linear models, such as the

use of logistic regression for binary outcomes, any omitted covariates will result in biased estimates of treatment effect.

Assessing treatment by covariate interactions in this review

Studies used in this assessment to evaluate whether or not different patient and/or disease characteristics are prognostic according to different treatments will include those used in the development of treatment-specific clinical prediction models, as well as randomised controlled trials (RCTs) and observational studies that include patients with differential treatment use at entry. The use of RCTs and observational studies is to acknowledge the evidence that these studies provide about differential treatment effects in the absence of treatment-specific clinical prediction models. Studies that provide information only about the prognostic effect of patient and/or disease characteristics are excluded; nevertheless, studies meeting the inclusion criteria do provide some, albeit selective, information about the prognostic effect of covariates according to treatment. However, the results should be treated with caution for the reasons given above.

The primary parameter of interest is that representing the interaction between treatment and baseline covariate; it is this parameter that quantifies whether or not the response to treatment varies according to the value of the covariate. In practice, such interactions should be assessed in a single regression model incorporating main effects and interaction terms.

As discussed previously, studies may lack sufficient power to detect interaction terms as being statistically significant [i.e. 95% confidence intervals (CIs) not including the null value] and it should not be assumed that absence of evidence is equivalent to evidence of absence. Similarly, in the event that a statistically significant treatment effect modifier is identified, it may not be clinically relevant. In addition, the results should be considered as hypothesis-generating, because studies were generally not designed to detect interaction effects; the potential treatment effect modifiers are assessed univariately in this review, although their relevance may be different when the correlation between multiple covariates is taken into consideration in clinical prediction models, and spurious results may occur by chance given the number of multiple comparisons being performed.

Interpretation of the evidence regarding patient and/or disease characteristics

There are four scenarios that may arise depending on whether a covariate is (or is not) prognostic for at least one treatment and whether a covariate is (or is not) a treatment effect modifier: these are illustrated below for a comparison of two treatments with respect to a single covariate, which may be discrete or continuous.

Scenario 1: prognostic variable for both treatments, but not a treatment effect modifier (*Figure 1*)

Given two treatments coded such that $t_1 = 0$ and $t_2 = 1$, the mean response (i.e. expected value) for a person with a baseline value of x_j who receives treatment t_1 is:

$$E[y_{ij}] = \beta_0 + \beta_1 x_j + \beta_2 t_i. \quad (2)$$

For treatment t_1 this is:

$$E[y_{1j}] = \beta_0 + \beta_1 x_j, \quad (3)$$

and for treatment t_2 this is:

$$E[y_{2j}] = (\beta_0 + \beta_2) + \beta_1 x_j. \quad (4)$$

In this scenario, the treatment effect is β_2, which is constant at each value of the predictor; it is also possible for a baseline variable to be a prognostic and for there to be no treatment effect (in which case, the two regression lines would be superimposed).

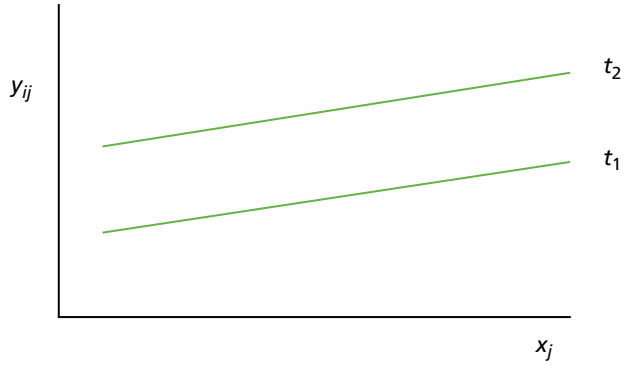

FIGURE 1 Scenario 1: prognostic variable for both treatments but not a treatment effect modifier.

Scenario 2: prognostic variable for both treatments and a treatment effect modifier (*Figure 2*)

Given two treatments coded such that $t_1 = 0$ and $t_2 = 1$, the mean response (i.e. expected value) for a person with a baseline value of x_j who receives treatment t_1 is:

$$E[y_{ij}] = \beta_0 + \beta_1 x_j + \beta_2 t_i + \beta_{12} t_i . x_j . \tag{5}$$

For treatment t_1 this is:

$$E[y_{1j}] = \beta_0 + \beta_1 x_j , \tag{6}$$

and for treatment t_2 this is:

$$E[y_{2j}] = (\beta_0 + \beta_2) + (\beta_1 + \beta_{12}) x_j . \tag{7}$$

In this scenario, the treatment effect at x_j is $\beta_2 + \beta_{12} x_j$, which depends on the value of the baseline variable; it is also possible that $\beta_2 = 0$.

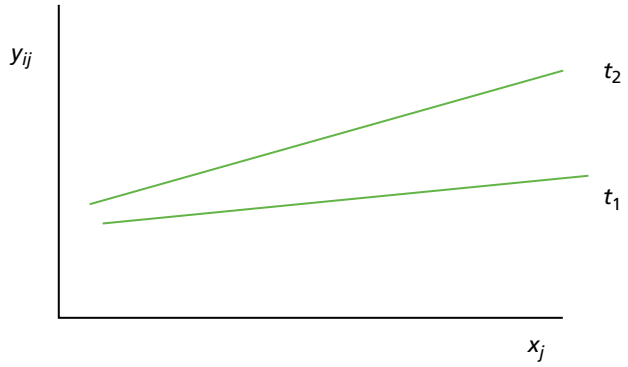

FIGURE 2 Scenario 2: prognostic variable for both treatments and a treatment effect modifier.

Scenario 3: not a prognostic variable for one treatment, but a treatment effect modifier (*Figure 3*)

Given two treatments coded such that $t_1 = 0$ and $t_2 = 1$, the mean response (i.e. expected value) for a person with a baseline value of x_j who receives treatment t_1 is:

$$E[y_{ij}] = \beta_0 + \beta_1 x_j + \beta_2 t_1 + \beta_{12} t_i . x_j . \tag{8}$$

For treatment t_1 this is:

$$E[y_{1j}] = \beta_0, \tag{9}$$

and for treatment t_2 this is:

$$E[y_{2j}] = (\beta_0 + \beta_2) + \beta_{12} x_j . \tag{10}$$

In this scenario, the treatment effect at x_j is $\beta_2 + \beta_2 x_j$, which depends on the value of the baseline variable; it is also possible that $\beta_2 = 0$.

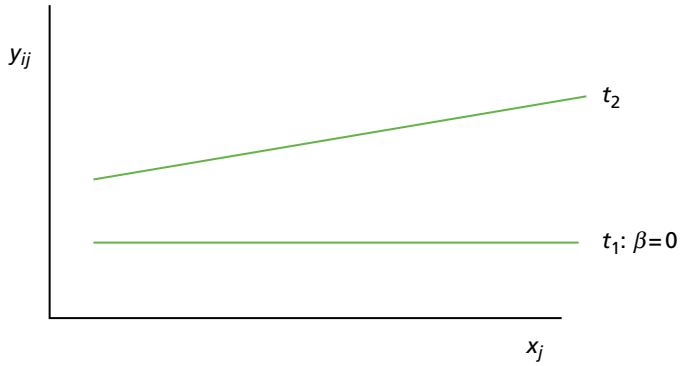

FIGURE 3 Scenario 3: not a prognostic variable for one treatment, but a treatment effect modifier.

Scenario 4: not a prognostic variable for either treatment and not a treatment effect modifier (*Figure 4*)

Given two treatments coded such that $t_1 = 0$ and $t_2 = 1$, the mean response (i.e. expected value) for a person with a baseline value of x_j who receives treatment t_1 is:

$$E[y_{ij}] = \beta_0 + \beta_1 x_j + \beta_2 t_i + \beta_{12} t_i . x_j . \tag{11}$$

For treatment t_1 this is:

$$E[y_{1j}] = \beta_0, \tag{12}$$

and for treatment t_2 this is:

$$E[y_{2j}] = \beta_0 + \beta_2 . \tag{13}$$

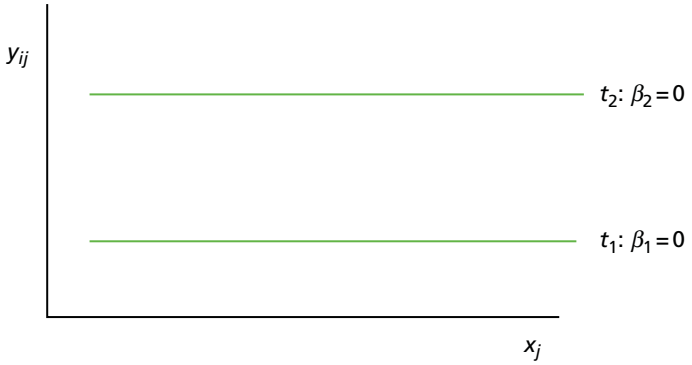

FIGURE 4 Scenario 4: not a prognostic variable for either treatment and not a treatment effect modifier.

In this scenario, the treatment effect at x_j is β_2, which is independent of the baseline variable; it is also possible for there to be no treatment effect (in which case, the two regression lines would be superimposed).

Stratified medicine research is concerned with identifying treatment effect modifiers, as illustrated by scenarios 2 and 3.

Chapter 2 Review question and objectives

Review question

The review question as outlined in the Health Technology Assessment (HTA) commissioning brief and final protocol was as follows: what test or combination of clinical, laboratory and imaging tests gives the best assessment of prognosis in RA, and how well do they predict response to treatment?

Assessment structure

The assessment structure consisted of systematic reviews with appropriate predefined subgroup analyses.

It was anticipated in the final protocol that the factors most likely to be of use for prognosis and prediction of treatment response would be assessed through meta-analysis of available aggregate-level data. The de novo development of a specific prediction model and the use of individual participant data (IPD) were outside the remit of this assessment.

Overall objectives of the assessment

The objectives of this work were to undertake systematic reviews to determine the:

- use of selected tests and assessment tools in the evaluation of prognosis in patients with early RA
- potential of selected tests and assessment tools as predictive markers of treatment response in patients with early RA.

Chapter 3 Methods for the assessment of prognosis and prediction of treatment response in early rheumatoid arthritis

Assessment structure

This assessment consisted of two related systematic reviews. The first systematic review (review 1, clinical prediction models) investigated the use of assessment tools and tests in the evaluation of prognosis in early RA patients. The second systematic review (review 2, prediction of treatment response) determined the ability of selected assessment tools and tests to predict the response to specific treatments.

The systematic reviews were informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.prisma-statement.org/) and current good practice in prognostic reviews, as advocated by the Cochrane Prognosis Methods Group (http://methods.cochrane.org/prognosis/).

A final protocol for this assessment was registered on PROSPERO (as record CRD42016042402).

Scoping of the assessment

The searches for reviews in this assessment were structured in two phases. The phase 1 scoping searches were performed to determine the approximate extent of the evidence base relevant to the assessment and to inform the discussion of prognostic and predictive variables for inclusion in conjunction with clinical advisors (full details are provided in *Appendix 1*).

Following discussions with two expert clinical advisors who manage patients with early RA in the UK (as described in *Acknowledgements*), the review team selected variables for inclusion. The selection of prognostic and predictive variables was based on:

- tests and assessment tools (e.g. selected laboratory tests, imaging tests and clinical assessment measures) the variables being readily available and used in UK clinical practice (and, therefore, genetic markers were not included by the review team)
- the clinical experience of advisors in evaluating prognosis/treatment response in patients
- the initial scoping of literature in the area by the review team.

The selected prognostic and predictive variables were used in the development of the full searches for reviews 1 and 2.

Justification of review approach

In view of the anticipated large number of search results, it was necessary for the review team to revise the intended review approach in order to maintain the feasibility of the assessment within the available resources and time scales. Additional details of protocol deviations are provided in *Appendix 2*.

Therefore, the two related systematic reviews were planned as detailed in the following sections.

Review 1: clinical prediction models

A systematic review of studies that describe the development, external validation or impact of eligible clinical prediction models in early RA was performed. As outlined in *Background to prognosis research*, prediction model research requires a multivariable analysis approach and, therefore, it was considered methodologically appropriate to restrict review 1 to the study of prognostic variables analysed in combination.

Review 2: prediction of treatment response

A systematic review of primary studies that describe the development, external validation or impact of eligible outcome models to predict treatment response in early RA patients was undertaken. Given that it was anticipated (based on earlier scoping searches) that the availability of outcome models and external validation studies relevant to review 2 would be limited, it was decided that review 2 would also include a review of studies to predict treatment response in patients with early RA. This approach would provide information for researchers who wish to develop outcome models for the prediction of treatment response based on a summary of the key evidence for the variables/tests and assessment tools selected following discussions with our clinical experts.

Methods for review 1 (clinical prediction models)

Identification of studies

Electronic databases

Studies were identified by searching the following electronic databases and research registers:

- MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and Epub ahead of print (via Ovid; 1947 to September 2016)
- EMBASE (via Ovid; 1974 to September 2016)
- The Cochrane Library (via Wiley Online Library), including Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), HTA databases (inception to September 2016, or 2015 in the case of DARE/NHS EED, which are no longer being updated)
- Web of Science Conference Proceedings (1990 to September 2016).

Sensitive keyword strategies using free text and, where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to disease (e.g. Arthritis, Rheumatoid/) and prognostic variables were combined with a highly sensitive search filter aimed at restricting results to prognostic studies.[44]

No date restrictions were used on any database. However, all searches were restricted to the English language because of time and resource constraints for translation services.

All resources were initially searched from inception to 27 September 2016. An example of the MEDLINE search strategy is provided in *Appendix 3*.

Research registers and other websites

The following resources were also searched for relevant evidence:

- The World Health Organization's trial search portal (http://apps.who.int/trialsearch) and ClinicalTrials.gov [(https://clinicaltrials.gov) records added since 2010 up to the date of the search on 27 September 2016].
- Arthritis Research UK; British Society for Rheumatology; National Rheumatoid Arthritis Society; Outcome Measures in Rheumatology (OMERACT) Task Force; Royal College of Pathologists; Royal College of Physicians; Royal College of Surgeons; EULAR, American College of Rheumatology; the US Food and Drug Administration (FDA); and the European Medicines Agency (EMA) (no date restrictions).

Results were manually added to EndNote Version X7 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] for sifting.

Other resources

To identify additional studies, the reference lists of all included studies and key systematic reviews were checked. In addition, key experts in the field were contacted.

Results from the phase 2 full searches were imported into reference management software EndNote and duplicates were removed.

Study selection

Studies were assessed for eligibility for review based on the following criteria.

Inclusion criteria

Population

Adult patients (aged ≥ 18 years) diagnosed with early RA. The final protocol stated that patients would be diagnosed with RA according to established criteria. Patients with early RA were defined in consultation with clinical advisors as being within 2 years of the onset of symptoms. It was noted that studies may report the duration of symptoms or the duration of disease at baseline and so the definitions applied in included studies were noted and tabulated. In the absence of any further information, disease duration at baseline was considered to be equivalent to symptom duration.

Studies investigating mixed populations were included only if ≥ 80% of the study population were early RA patients or if subgroup data were presented for this population.

Externally validated clinical prediction models were included if the external validation population met the inclusion criteria, even if the original development population did not meet the inclusion criteria. The rationale for this was that a clinical prediction model might perform well for the decision problem and it is not important that it was originally developed in a different population. In this case, the study that developed the original clinical prediction model was included even if it did not meet the criteria stated above. In addition, studies proposing clinical prediction models that did not present internal validation were included if they had been externally validated in another study. External validations in populations outside the scope of the assessment were not included in the review, but were referred to in the discussion as appropriate.

Technology

Blood tests, imaging modalities and clinical assessment scores used in the evaluation of prognosis in patients with early RA were included. Specific tests and assessment tools to be included were determined following the phase 1 scoping searches and agreed with clinical advisors. Tests and assessment tools were for the measurement of prognostic variables as described below.

Prognostic variables

Prognostic variables considered in the assessment were informed by the phase 1 scoping searches and agreed following discussion between the review team and clinical advisors. The prognostic variables selected for inclusion for review 1 were:

- anticitrullinated protein/peptide anti-bodies (ACPAs) status; RF status
- erosions/joint damage as assessed on radiographs
- C-reactive protein levels
- erythrocyte sedimentation rate
- SJC
- DAS28
- early RA untreated for ≥ 12 weeks following the onset of symptoms

- smoking
- HAQ scores.

Genetic markers were discussed in the assessment only when these were included in a final clinical prediction model alongside other eligible prognostic factors as selected by the review team in collaboration with the clinical advisors. This was decided on the basis that genetic testing is not currently used in routine UK clinical practice.

Included clinical prediction models contained at least one eligible prognostic variable. Results were presented based on all prognostic variables included in each multivariable model (including those not included in this review).

Outcomes

The selected outcomes considered in this assessment were agreed following discussions between the review team and the clinical advisors. The outcomes below were considered by the review team and the clinical advisors to have clinical relevance and to be important to patients, and are widely reported in RA research. The outcomes selected for inclusion in review 1 were:

- disease activity as measured by the DAS28
- physical function as measured by the HAQ
- joint damage as assessed on radiographs.

Study types

It was anticipated in the final protocol that the study types included in review 1 would be likely to include published reports of cohort studies (and potentially case–control studies), which report the associations between individual prognostic variables and outcomes. However, as described above, in order to maintain the feasibility of the assessment, review 1 was restricted to the inclusion of studies that describe the development, external validation or the impact of eligible clinical prediction models in early RA.

Included studies were categorised in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) classification, which groups studies according to their methods of determination of performance.

Studies developing clinical prediction models that had not been validated in one of the included external validation studies were included if they presented some form of internal validation to quantify predictive performance [e.g. calibration and discrimination measures, such as the *c*-statistic or area under the curve (AUC)]. For clinical prediction models that were not externally validated and did not report the *c*-statistic or AUC or calibration, a study reporting at least two alternative measures of predictive performance [e.g. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy] was considered to be eligible on the basis of being sufficiently informative to the review. When a study reported only R^2 (a measure of the model goodness-of-fit), this was not considered to provide sufficient information regarding predictive performance, and the study was not included (but recorded in the table of excluded full-text studies in *Appendix 4*).

Exclusion criteria

The following criteria were applied to exclude studies:

- non-English-language papers
- reports published as meeting abstracts only, in which insufficient methodological/results details are reported
- animal models
- preclinical and biological studies
- narrative reviews, editorials and opinions.

It was necessary, because of resource and time constraints, to deviate from the final protocol in the applied screening approach (see *Appendix 1*). An iterative approach to the screening of evidence was undertaken (adapted from Archer *et al.*[45]). Titles and abstracts of search records were examined by one reviewer. Titles and abstracts were searched for terms relating to clinical prediction models. Key terms were identified by consulting publications relating to prediction model research (e.g. Moons *et al.*,[31] Debray *et al.*[40]). Terms used were risk model*, prognostic model*, prediction model*, predictive model*, risk assessment model*, prediction score*, algorithm*, matrix/matrices, assessment tool*, prediction rule*, decision rule*, and risk score* in order to identify potentially relevant studies for screening at the full-text stage. As described previously, this method was supplemented by the hand-searching of reference lists of included studies, existing key systematic reviews (e.g. Bombardier *et al.*,[46] Navarro-Compán *et al.*[47]), contact with clinical experts and the searching of grey literature.

Full texts of remaining articles were screened for eligibility before inclusion. Study inclusion based on full-text articles was performed by one reviewer and queries were discussed with a second reviewer. Any discrepancies were resolved by discussion, with the involvement of a third team member when required.

Data extraction

A data extraction form was designed and piloted before use on a minimum of two studies.

Data were extracted by one reviewer. Extracted data were checked for accuracy by a second reviewer. Any discrepancies were discussed and resolved, with reference to a third team member when required.

The CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[48] includes guidance on the relevant items for extraction from reports of prediction modelling studies. Data extraction was guided by CHARMS.[48] Predictive performance measures relating to each clinical prediction model's overall performance, calibration and discriminative ability were extracted from each clinical prediction model development and external validation study. Following advice in Debray *et al.*,[40] the *c*-statistic was used as the primary measure of discrimination and the O : E ratio used as the primary measure of calibration. If these measures or the associated variance estimates were not reported for a particular study, they were computed from other information when possible. The results of the Hosmer–Lemeshow test (a measure of model calibration) were also extracted, along with measures of model overall goodness of fit (such as R^2). Information regarding the case mix of the development/validation population, which may help to explain the heterogeneity in the results, was also summarised from the available information when possible. Further details relating to the data extraction and associated calculations are provided in *Appendix 5*.

Quality assessment strategy

The assessment of the study quality characteristics of clinical prediction modelling studies was informed by criteria included in an unpublished draft version of the Prediction model study Risk Of Bias Assessment Tool (PROBAST).[49] The risks of bias for participant selection, predictors and outcomes were discussed narratively and tabulated. Potential key sources of bias in the model development and validation were discussed narratively.

The methodological quality of each included study was assessed by one reviewer and checked with a second reviewer. Disagreements were resolved by discussion between the two reviewers and if agreement could not be reached, a third reviewer was consulted.

Synthesis methods

Data relating to clinical prediction model performance were described in a narrative synthesis, presented separately for internal and external validation studies. An evidence synthesis using meta-analysis was considered for external validation studies.

Variation in predictive performance is expected because of differences in the design and execution of alternative external validation studies and, hence, a random-effects (RE) model that accounts for between-study heterogeneity was used.[40] Results using a fixed-effects (FE) model (i.e. a condition inference given the observed studies) are also presented for comparison.

Results are presented in terms of the summary *c*-statistic (and 95% CIs) that quantifies the average performance across the included studies. For RE models, it was anticipated that an estimate of the between-study SD (that quantifies the extent of heterogeneity between studies), as well as the 95% prediction intervals (which provide a range for the potential model performance in a new study), would also be provided. However, this was not possible on account of the limited number of studies that validated each prediction model, thereby providing limited information with which to estimate the between-study heterogeneity.

All analyses were conducted in R[50] (The R Foundation for Statistical Computing, Vienna, Austria) using the metafor package.[51] A restricted maximum likelihood estimation was used with the Hartung–Knapp–Sidik–Jonkman method (which accounts for uncertainty in the estimated between-study heterogeneity) to estimate the CIs for the pooled estimate and the 95% prediction intervals.[40,52] Analysis was conducted on the logit scale as previously recommended and back-transformed to the original scale for the presentation of results.[40,52]

It was stated in the review protocol that meta-analyses would be conducted using a Bayesian RE model. However, this was modified for the final analysis, because there were very few studies that validated each clinical prediction model, thereby providing limited information with which to estimate the between-study heterogeneity. Although it would be possible to implement a Bayesian RE analysis using a weakly informative prior, this was not implemented, because there was a lack of empirical evidence to inform the prior distribution for the heterogeneity parameter and eliciting experts' beliefs was beyond the scope of this project. Although the analysis deviated slightly from the protocol, the implemented RE model accounts for uncertainty in the between-study heterogeneity and is consistent with methodological recommendations.[40]

Given the limited number of studies available, it was not possible to explore heterogeneity in prognostic/predictive effects using metaregression. However, subgroup analyses based on baseline DAS28 were considered in the narrative synthesis of evidence for review 1 and review 2.

Methods for review 2 (prediction of treatment response)

Identification of studies

Electronic databases

Electronic databases, research registers and other websites searched were identical to those for review 1 (see *Identification of studies*). Sensitive keyword strategies using free text and, when available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. The disease and candidate variable terms used in review 1 were combined with the appropriate search filter for review 2.[53]

Research registers and other websites

The resources searched were identical to those used in review 1. The results were manually added to EndNote for sifting.

Other resources

To identify additional studies, the reference lists of all included studies were checked. Hand-searching of key systematic reviews and narrative reviews was also performed. A citation search of included articles

[using Google Scholar (Google Inc., Mountain View, CA, USA)] was undertaken. In addition, key experts in the field were contacted.

Results from the phase 2 full searches were imported into reference management software EndNote (version X8) and duplicates were removed.

Study selection

Studies were assessed for eligibility for review 2 based on the following criteria.

Inclusion criteria

Population

Adult RA patients (aged ≥ 18 years) who have:

- received treatment with cDMARDs/bDMARDs for RA
- baseline/early disease and follow-up data for selected variables (as defined below).

For the review for the prediction of treatment response (review 2), response to cDMARDs and bDMARDs was studied. It was planned in the final protocol for review 2 that, if data allowed, treatment would be subdivided into cDMARDs and bDMARDs. Response to any other treatments (e.g. steroids) was not assessed for reasons of feasibility. Predictors of treatment response to individual drugs (e.g. specific biologics) would be explored if feasible and if sufficient evidence was available.

Studies were eligible for inclusion in review 2 if they involved at least 6 months' treatment duration (with the exception of certolizumab pegol, for which the response is largely known at 12 weeks and, therefore, a 12-week treatment duration was considered to be more acceptable by clinical advisors and was applied for this drug).

Technology

The tests and assessment tools for the measurement of predictive variables are as described below.

Predictive variables

The predictive variables considered in the assessment were also informed by phase 1 scoping searches and selected following discussion between the review team and clinical advisors. The predictive variables selected for inclusion in review 2 were the same as those for review 1, with the addition of two variables:

1. body mass index (BMI)
2. vascularity of synovium assessed using power Doppler ultrasound (PDUS).

Outcomes

The outcomes selected for inclusion were the same as for review 1, with the addition of:

- definitions of response/remission selected in conjunction with clinical advisors (EULAR response; remission: a DAS28 of < 2.6, a Disease Activity Score (DAS) of < 1.6 or ACR/EULAR remission).

Study types

It was anticipated in the protocol that the included study types in review 2 would be cohort studies and RCTs. Following a protocol amendment, in order to maintain the feasibility of the assessment within the available time and resources, review 2 consisted of:

- a systematic review of studies that describe the development, external validation or impact of eligible clinical prediction models to predict the response to individual treatments in patients with early RA (developed/validated in observational cohorts or experimental data sets)

- a review of primary studies (experimental or observational) to identify patient characteristics that affect the response to individual treatments in patients with early RA.

The exclusion criteria were as described for review 1.

The titles and abstracts of search records were examined by one reviewer and irrelevant evidence was excluded. The full texts of remaining articles were screened for eligibility before inclusion. Study inclusion based on full-text articles was performed by one reviewer and queries were discussed with a second reviewer. Any discrepancies were resolved by discussion, with the involvement of a third team member when required.

Data extraction

A data extraction form was designed and piloted before use on a minimum of two studies.

Data were extracted by one reviewer. Extracted data were checked for accuracy by a second reviewer. Any discrepancies were discussed and resolved, with reference to a third team member when required.

Quality assessment strategy

Any identified clinical prediction model studies were to be critically appraised, guided by the items included in the PROBAST.[49] Studies of prognostic variables were assessed by criteria informed by the Quality in Prognosis Studies (QUIPS) tool (see Hayden *et al.*[54]), as stated in the final protocol.

Critical appraisal was performed by one reviewer and double-checked by a second reviewer. Discrepancies were resolved by discussion, with the involvement of a third team member if necessary.

Synthesis methods

In the protocol, it was envisaged that a formal meta-analysis comparing all treatments across all studies would be performed with respect to the predictive ability of treatments. However, for specific outcome measures and potential treatment effect modifiers, there were no studies that shared any treatments in common. Consequently, a formal meta-analysis was not performed and the results are presented assessing the predictive ability of treatments by study.

Some authors fitted single regression models to the data from all treatment groups and included only the main effects of treatment and baseline covariates; these models do not allow an assessment of the interaction between treatments and baseline covariates. Other authors fitted separate regression models to the data from each treatment group and presented estimates of treatment effects by covariate; it is these estimates that are used to quantify the extent to which the treatment effect varies by covariate.

For continuous outcomes, the interaction effect is estimated by calculating the difference (and 95% CI for the difference, when possible) in the mean between treatments; departures from zero are indicative of the covariate being a treatment effect modifier. For binary outcomes, the interaction is estimated by calculating the ratio (and 95% CI for the ratio when possible) of the ORs between treatments; departures from one are indicative of the covariate being a treatment effect modifier.

Results indicating that a covariate is not a treatment effect modifier should not be interpreted to mean that a covariate is prognostic, only that the relationship between covariate and response may be the same for both treatments subject to a treatment effect (i.e. the covariate may be prognostic for both treatments or not prognostic for both treatments).

Chapter 4 Results: review 1

Quantity of research available

Searches for evidence (*Figure 5*) identified 22 model development studies and one combined model development/external validation study, reporting a total of 39 clinical prediction models for the prediction of major outcomes, including radiographically assessed joint damage, the HAQ score and the DAS28 (note that one publication[56] considered the development of models for multiple outcomes; however, because of unclear reporting, the individual models could not be summarised and so have been counted as a single entry for the purposes of the assessment). The study by Bombardier *et al.*[57] was available as a conference abstract only and a full-text publication was not available. Six external validation studies (including the combined model development/external validation study) of eight previously proposed clinical prediction

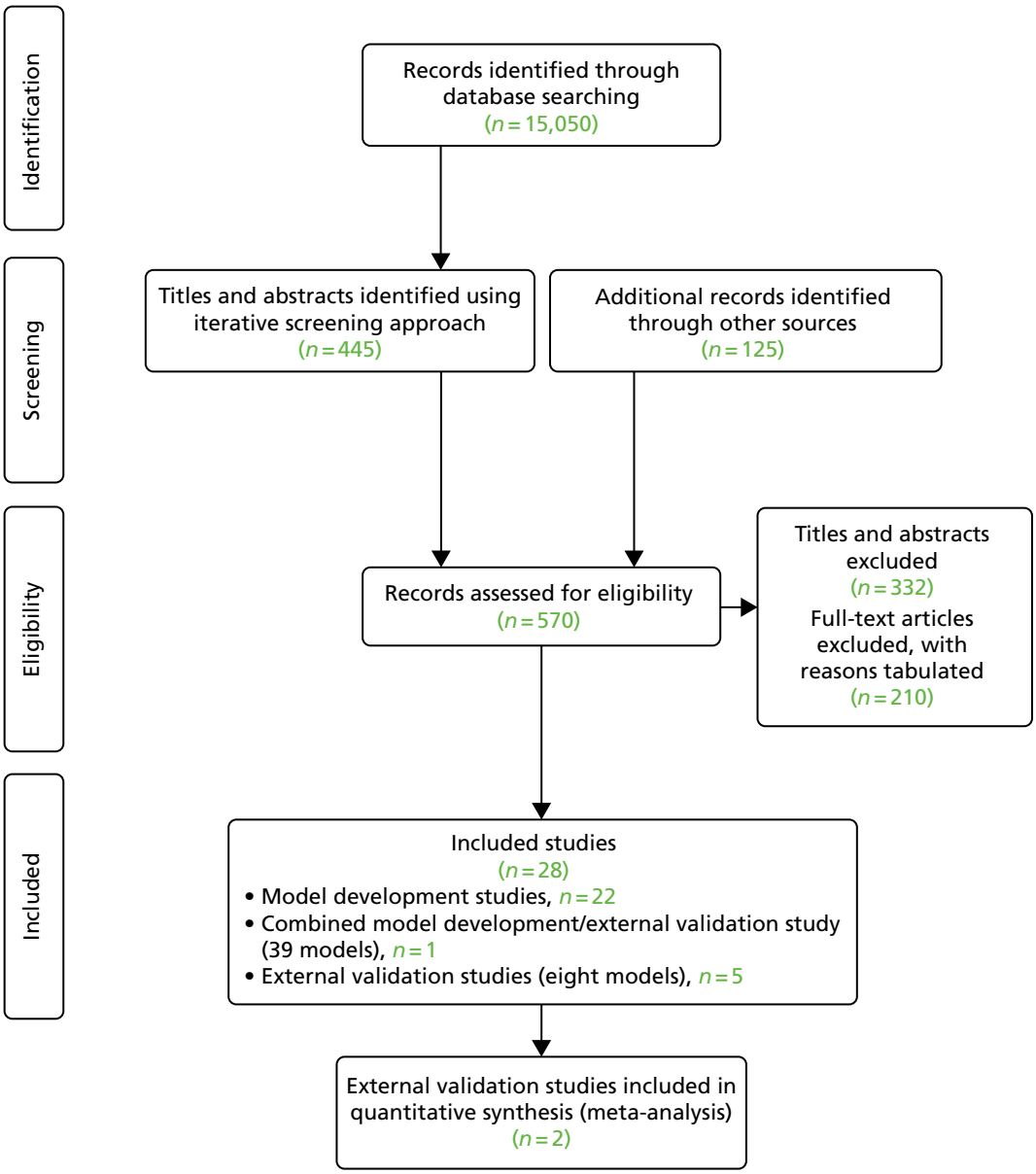

FIGURE 5 Review 1: study selection represented as an adapted PRISMA flow diagram.[55]

models for radiographically assessed joint damage outcomes were identified. No studies assessing the impact of the use of clinical prediction models in the clinical management of early RA were identified.

Quality of the research available

Potential sources of bias in participant selection, predictors, outcomes, model development and validation are discussed in the following sections and tabulated in *Appendix 6*.

Types of included prediction model studies

The TRIPOD statement[26] was developed with the aim of improving the quality of reporting of prediction model studies. Collins *et al.*[26] described six categories (listed below) that can be used to classify studies according to their aim (development or/and validation) and the methodology used.

The inclusion criteria for review 1 required that studies developing clinical prediction models apply some form of internal validation to quantify the predictive performance of the developed model (e.g. calibration and discrimination), with the exception of cases in which the clinical prediction model had been subsequently externally validated. In these cases, the external validation results may be considered to be more informative than the omitted internal validation results and it was deemed necessary to include the original development paper for completeness. These studies did not have a category according to the TRIPOD statement, and it was therefore necessary to introduce a new TRIPOD category (Type 0) to allow the description of these studies.

The tailored TRIPOD classification categories used in this review (based on Collins *et al.*[26]) are as follows:

- Type 0 – development of a clinical prediction model in which the predictive performance is not evaluated in the development paper, but an evaluation of the predictive performance has been considered in a separate publication.
- Type 1a – development of a clinical prediction model with an evaluation of the predictive performance using the same data set (apparent performance).
- Type 1b – development of a clinical prediction model using the whole data set and an evaluation of the predictive performance using resampling (e.g. bootstrapping or cross-validation).
- Type 2a – random splitting of data into two groups, the first for clinical prediction model development and the second for the testing of its predictive performance.
- Type 2 – non-random splitting of data into two groups, the first for clinical prediction model development and the second for the testing of its predictive performance.
- Type 3 – development of a clinical prediction model in one data set and an evaluation of the predictive performance on separate data (e.g. from a different study).
- Type 4 – the evaluation of the predictive performance of an existing clinical prediction model using separate data (external validation).

The TRIPOD classification categories of the 28 included studies are presented in *Table 1*. The PROBAST[49] study-type classifications of the included studies are also presented in *Table 1*.

Of the 23 clinical prediction model development studies, the vast majority ($n = 16$) were TRIPOD type 1a {i.e. Berglin *et al.*,[59] Visser *et al.*[79] [Behandelings Strategie (BeSt)], Combe *et al.*[62] (Combe A), Combe *et al.*[63] (Combe B), de Vries-Bouwstra *et al.*,[65] Degboé *et al.*,[66] Dirven *et al.*,[67] Drossaers-Bakker *et al.*,[56] Fautrel *et al.*[69] [Études et suivi des polyarthrites indifférenciées récentes (ESPOIR)], Forslind *et al.*,[70] Graell *et al.*,[71] Houseman *et al.*,[72] Saevarsdottir *et al.*[73,74] [Swedish Farmacotherapy (SWEFOT)], Sanmartí *et al.*,[75] Syversen *et al.*[76] and van Steenbergen *et al.*[77]}, with validation conducted in exactly the same data as those used for clinical prediction model development. Fewer studies were categorised as type 1b ($n = 1$; i.e. Bansback *et al.*[58]),

TABLE 1 The TRIPOD classification of included studies

First author (year of publication)	Name of clinical prediction model[a]	Externally validated? (Y/N)	Model presented in useable format?	Category	
				PROBAST	TRIPOD[b]
Clinical prediction model development studies					
Bansback (2006)[58]	Bansback	N	Y	Development only	1b
Berglin (2006)[59]	Berglin	N	N	Development only	1a
Bombardier (2009)[57]	SONORA	Y	N	Development only	0
Brennan (1996)[60]	Brennan	N	Y	Development only	2a
Centola (2013)[61]	Centola	Y	Y	Development only	0
Combe (2001)[62]	Combe (A)	N	Y	Development only	1a
Combe (2003)[63]	Combe (B)	N	N	Development only	1a
de Punder (2015)[64]	de Punder	N	Y	Development/external validation	1b/4
de Vries-Bouwstra (2006)[65]	de Vries-Bouwstra	N	N	Development only	1a
Degboé (2015)[66]	Degboé	N	N	Development only	1a
Dirven (2012)[67]	Dirven	N	Y	Development only	1a
Dixey (2004)[68]	Dixey	N	N	Development only	2a
Drossaers-Bakker (2002)[56]	Drossaers-Bakker	N	N	Development only	1a
Fautrel (2012)[69]	ESPOIR	Y	Y	Development only	1a
Forslind (2004)[70]	Forslind	N	Y	Development only	1a
Graell (2009)[71]	Graell	N	Y	Development only	1a
Houseman (2012)[72]	Houseman	N	N	Development only	1a
Saevarsdottir (2015)[73,74]	SWEFOT	Y	N	Development/external validation	1a/4
Sanmartí (2007)[75]	Sanmartí	N	Y	Development only	1a
Syversen (2008)[76]	Syversen	Y	Y	Development only	1a
van Steenbergen (2015)[77]	van Steenbergen	N	N	Development only	1a
Vastesaeger (2009)[78]	ASPIRE	Y	Y	Development and external validation	3[c]
Visser (2010)[79]	BeSt	Y	Y	Development only	1a
External validation studies					
De Cock (2014)[80]				External validation only	4
Granger (2016)[82]				External validation only	4
Hambardzumyan (2015)[83]				External validation only	4
Heimans (2015)[84]				External validation only	4
Markusse (2014)[85]				External validation only	4

ASPIRE, Active controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset; BeSt, Behandelings Strategie; ESPOIR; European Clinical Study for the Application of Regenerative Heart Valves; N, no; SONORA, Study Of New-Onset Rheumatoid Arthritis; SWEFOT, Swedish Farmacotherapy; Y, yes.

a Selected studies presented multiple alternative models. These are described in *Table 8*.

b The TRIPOD categories are as described in *Types of included prediction model studies*.

c The validation population (established RA) was outside the scope of the assessment.

using techniques to evaluate performance and optimism of the developed model, type 2a ($n = 2$; i.e. Brennan *et al.*[60] and Dixey *et al.*[68]), using a data-splitting approach for development and validation, or type 0 {$n = 2$; i.e. Bombardier *et al.*[57] [Study Of New-Onset Rheumatoid Arthritis (SONORA)] and Centola *et al.*[61]}, with no internal validation presented for Bombardier *et al.*[57] Although internal validation was conducted for Centola *et al.*,[61] it was developed for a different outcome measure and so the study is categorised as type 0 for the purpose of the current review. One study {$n = 1$; i.e. Vastesaeger *et al.*[78] [Active controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset (ASPIRE)]} considered validation in an external population in addition to model development (type 3); however, the external validation population comprised patients with established RA and, therefore, was outside the scope of this assessment. The methods of internal validation and reporting of models in the included development studies are described in greater detail in *Model development*.

Five additional included studies were external validations of clinical prediction models (TRIPOD class 4). Three of these studies (i.e. De Cock *et al.*,[80] Granger *et al.*[82] and Heimans *et al.*[84]) externally validated a total of seven clinical prediction models (i.e. ASPIRE CRP,[78] ASPIRE ESR,[78] BeSt,[79] ESPOIR,[69] SONORA,[57] SWEFOT[73] and Syversen[76]). The remaining two external validation studies (Hambardzumyan *et al.*[83] and Markusse *et al.*[85]) evaluated the use of a multibiomarker disease activity (MBDA) test[61] (developed as a measure of disease activity) in the prediction of eligible clinical outcomes. In addition to the seven purely external validation studies, the de Punder model development paper[64] (TRIPOD category 1b/4) also externally validated the BeSt[79] and ESPOIR[69] models.

Two additional external validation studies were identified but not included.[73,86] The study reported by Durnez *et al.*[86] is considered to be a precursor study to the work by De Cock *et al.*,[80] and so the work by De Cock *et al.*[80] is utilised in this assessment as being more recent and comprehensive in the coverage of validated models. The application of the BeSt model[79] was considered by Saevarsdottir *et al.*[73] (TRIPOD category 1a/4) using the SWEFOT data set. However, the presented results did not provide sufficient data to be considered as informative to the current review, as no summary statistic of overall performance (e.g. *c*-statistic) was reported. Saevarsdottir *et al.*[73] presented the allocation of individuals to risk matrix categories, combined for the whole validation sample rather than separately by treatment group.

Description of data sources for the development of clinical prediction models and external validation

Moons *et al.*[31] advocated the use of cohort study data in the development of clinical prediction models, which are preferably prospective in design to allow for the greater completeness of data collection.[31] Trial data are also an appropriate data source, although it has been noted that trial eligibility criteria may result in more restricted and less generalisable data than registry cohort studies.[31] All identified clinical prediction models for review 1 were developed in either observational cohort or registry data or in existing cohorts from intervention trials in early RA populations and, therefore, can be considered to have been developed in appropriate data sources. Studies were longitudinal in design, with potential predictors measured in an early RA population at baseline or in an early disease stage before the measurement of a specified outcome at a subsequent time point. There was one main exception to this, Houseman *et al.*,[72] which is discussed further in *Description of predictors*. The characteristics of the data sources used in the development and external validation of the included clinical prediction models are tabulated in *Table 2*.

Four included clinical prediction model development studies used RCT data.[67,73,78,79] The models by Vastesaeger *et al.*[78] were developed in the ASPIRE RCT.[87] Both the models by Visser *et al.*[79] and Dirven *et al.*[67] were generated using data from the BeSt RCT.[89] Data from the SWEFOT RCT[90] were used by Saevarsdottir *et al.*[73] to build the SWEFOT clinical prediction model.

The Leiden Early Arthritis Clinic cohort was a common data source, being used in the development of models by de Vries-Bouwstra *et al.*,[65] Drossaers-Bakker *et al.*[56] and van Steenbergen *et al.*[77] The ESPOIR cohort was

TABLE 2 Data sources used in the development and external validation of the included risk prediction models

Name of clinical prediction model/external validation	Name and study design of data source	Setting (number of centres) and period of data collection	Key eligibility criteria
Clinical prediction model development studies			
ASPIRE[78]	Active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset (ASPIRE) RCT[87] Internally validated in the anti-TNF trial in rheumatoid arthritis with concomitant therapy (ATTRACT)[88] [median disease duration, 8.4 years (IQR 4.3–14.7 years); established RA outside scope of assessment]	Multicentre, multinational study (122 sites in North America and Europe) Patients recruited between 2000 and 2002	Aged 18–75 years, met the 1987 revised ACR criteria, persistent synovitis for 3 months to 3 years, ≥ 10 swollen joints and ≥ 12 tender joints. Plus one or more of positive serum RF, radiographically detected erosions of hands/feet or CRP level of ≥ 2.0 mg/dl. Patients excluded if any prior MTX (three or fewer pre-study doses permitted), received other DMARDs within 4 weeks of entry (or LEF within past 6 months) or treated with IFX, ETN, ADA or other anti-TNF Subjects were excluded if they were infected with HIV, hepatitis B or hepatitis C, they had a history of active or past TB, congestive heart failure, lymphoma or other malignancy within the past 5 years (excluding excised skin cancers)
Bansback[58]	Early Rheumatoid Arthritis Study (ERAS) inception cohort	Unspecified regions of England (nine centres) Cohort established in 1986	All consecutive RA patients seen within 2 years of initial symptoms and before second-line drug use. Patients completing 5 years of follow-up included in the analysis
Berglin[59]	Cohort data	Department of Rheumatology, University Hospital, Umeå, Sweden, co-analysed with Northern Sweden Health and Disease Study (NSHDS) cohort and maternity cohort of northern Sweden (Medical Biobank), Umeå, Sweden (number of centres and period of data collection NR)	Department of Rheumatology, University Hospital, Umeå register: early RA (duration of < 1 year) meeting the 1987 revised ACR criteria for RA, with a known date of the onset of symptoms

continued

TABLE 2 Data sources used in the development and external validation of the included risk prediction models (*continued*)

Name of clinical prediction model/external validation	Name and study design of data source	Setting (number of centres) and period of data collection	Key eligibility criteria
BeSt[79]	Behandelings Strategie (BeSt) RCT[89]	18 peripheral and two university hospitals in the western Netherlands Patients recruited between 2000 and 2002	Early RA defined by the 1987 revised ACR criteria, disease duration of ≤ 2 years, aged ≥ 18 years, active disease with ≥ 6 of 66 swollen joints, ≥ 6 of 68 tender joints and either an ESR of ≥ 28 mm/hour or a global health score of ≥ 20 mm on a 0- to 100-mm VAS (0 = best, 100 = worst) Subjects were excluded if they had previous DMARD treatment other than antimalarials, concomitant treatment with an experimental drug, malignancy within the past 5 years, bone marrow hypoplasia, serum aspartate aminotransferase or alanine aminotransferase (ALT) levels of > 3 times the upper limit of normal level, serum creatinine levels of > 150 µm/l or estimated creatinine clearance of < 75 ml/minute, diabetes mellitus, alcohol or drug abuse, concurrent pregnancy, wish to conceive during study period or inadequate contraception
Brennan[60]	Prospective cohort	All primary care general practices in Norwich Health Authority, Norfolk, UK (number of centres NR) Recruited between 1990 and 1993	Satisfied any subset of the revised 1987 ACR RA criteria and were recruited within 180 days of the onset of symptoms, with complete baseline and 1-year follow-up measurements (and having provided blood for RF testing at baseline)
Centola[61]	Feasibility studies (stage 2): Oklahoma City cohort and Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS) cohort Algorithm training study (stage 3): Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS) cohort and Index for Rheumatoid Arthritis Measurement (InFoRM) study	NR	All patients met ≥ 4 of 7 of the 1987 revised ACR criteria for RA

Name of clinical prediction model/external validation	Name and study design of data source	Setting (number of centres) and period of data collection	Key eligibility criteria
Combe (A)[62]	Prospective cohort	France (four centres: Montpellier, Paris-Cochin, Toulouse and Tours) Included March 1993 to October 1994	All consecutive outpatients referred from primary care, disease duration of < 1 year, met ACR criteria for RA, DMARD-naive
Combe (B)[63]	Prospective cohort	France (four centres: Montpellier, Paris-Cochin, Toulouse, Tours) Included March 1993 to October 1994	All consecutive outpatients referred from primary care, disease duration of < 1 year, met ACR criteria for RA and were DMARD naive
de Punder[64]	Nijmegen early RA inception cohort	Radboud University Medical Centre, Nijmegen, the Netherlands Included from 1985 to 2008	Satisfied the 1987 ACR criteria for RA, disease duration of ≤ 1 year, no previous DMARD use and aged ≥ 18 years. Patients with radiographs available at inclusion and after 2 or 3 years' follow-up included in analysis Patients treated with biologic DMARDs within first 3 years were excluded from analysis
de Vries-Bouwstra[65]	Leiden Early Arthritis Clinic cohort	Early Arthritis Clinic (EAC), Department of Rheumatology, Leiden University Medical Centre, the Netherlands Sample from patients included from 1993 to 1999	Arthritis confirmed by rheumatologist, duration of symptoms of < 2 years and patient had not seen another rheumatologist for the same symptoms. All patients presenting with RA/probable RA and in whom a diagnosis of RA was confirmed at 3 months after presentation. Follow-up of ≥ 1-year and radiographs of hands and feet at baseline and after 1 year included in analysis. Definite RA according to the 1987 revised ACR criteria but without the criterion that symptoms must be of 6 weeks' duration and observed by a physician
Degboé[66]	ESPOIR cohort	14 regional centres, France Period of data collection NR	Suspected or confirmed RA diagnosis, aged 18–70 years, ≥ 2 swollen joints for > 6 weeks and < 6 months, no receipt of DMARDs or steroids except for < 2 weeks prior to entry. Included in analysis if satisfied the 2010 ACR/EULAR criteria and with complete radiographs at baseline and year 1 and complete ACPA measurements

continued

TABLE 2 Data sources used in the development and external validation of the included risk prediction models (*continued*)

Name of clinical prediction model/external validation	Name and study design of data source	Setting (number of centres) and period of data collection	Key eligibility criteria
Dirven[67]	Behandelings Strategie (BeSt) RCT[89]	The Netherlands Number of centres and period of data collection NR	DMARD-naive patients, with RA as defined by the 1987 revised ACR criteria
Dixey[68]	Inception cohort	Rheumatology departments of nine hospitals, country NR, but assumed to be the UK Recruitment of patients from 1986	Patients with RA according to the 1987 revised ACR criteria, duration of symptoms of ≤ 2 years, no use of second-line medication. Patients completing 3 years' follow-up with adequate-quality radiographs for scoring were included in the analysis
Drossaers-Bakker[56]	Prospective inception cohort Leiden Early Arthritis Clinic cohort	Rheumatology outpatient clinic of Leiden University Medical Centre, the Netherlands Patients attending from 1982 to 1986	All consecutive female RA patients, with symptoms of < 5 years' duration, aged 20–50 years at first visit
ESPOIR[69]	ESPOIR cohort	14 regional centres in France (16 university hospital rheumatology departments) Patients referred and included from December 2002 to March 2005	Patients recruited from the community, with early arthritis for < 6 months, aged 18–70 years, two or more swollen joints for > 6 weeks and < 6 months, suspected/confirmed RA diagnosis, not receiving any DMARDs or steroids except for < 2 weeks before entry. Current study included ESPOIR patients with RA diagnosis according to the rheumatologist and receipt of first cDMARD with demonstrated efficacy for ≥ 3 months of the first year of follow-up
Forslind[70]	BARFOT (Better Anti-Rheumatic Farmacotherapy) prospective cohort	Sweden (multicentre observational study, number of centres NR) Cohort recruited from July 1993 to June 1997	RA satisfying the 1987 revised ACR criteria, with a disease duration of ≤ 1 year

Name of clinical prediction model/external validation	Name and study design of data source	Setting (number of centres) and period of data collection	Key eligibility criteria
Graell[71]	Prospective cohort	Rheumatology units of Hospital Clinical of Barcelona and Hospital Parc Tauli of Sabadell, Spain Patients recruited from 1998 to 2003	Patients met the 1987 revised ACR criteria; symptoms for < 24 months, patients previously treated with DMARDs or > 10 mg/day of prednisone were excluded
Houseman[72]	Prospective cohort	Geographical setting and number of centres NR (general rheumatology clinics) Cohort established between 1998 and 2000	Consecutive early RA patients recruited from general rheumatology clinics and from among patients referred for early synovitis. Satisfied the 1987 revised ACR criteria for RA with the onset of persistent symptoms for < 2 years
Sanmartí[75]	Prospective cohort	Rheumatology units of Hospital Clinical of Barcelona and Hospital Parc Tauli of Sabadell, Spain Patients recruited from 1998 to 2003	Patients met the 1987 revised ACR criteria; symptoms for < 24 months, patients previously treated with DMARDs or > 10 mg/day of prednisone were excluded
SONORA[57]	SONORA cohort	North America	Patients diagnosed by rheumatologist with early RA (i.e. a symptom duration ≥ 3 and ≤ 12 months)
SWEFOT[73]	SWEFOT RCT	15 rheumatology units in Sweden[90] Patients screened for inclusion from 2002 to 2005[90]	RA according to the 1987 revised ACR criteria, aged ≥ 18 years, with symptom duration for < 1 year, a DAS28 of > 3.2, no previous DMARDs and stable prednisolone dose if present for ≥ 4 weeks before entry and throughout the study at ≤ 10 mg/day
Syversen[76]	Prospective cohort European Research on Incapacitating Disease and Social Support (EURIDISS) project	Geographical setting, number of centres NR EURIDISS began in 1992	Clinical diagnosis of RA (1987 ACR criteria), aged 20–70 years, with a disease duration of 0–4 years at baseline Patients with Steinbrocker function class IV excluded
van Steenbergen[77]	Prospective cohort Leiden Early Arthritis Clinic cohort	Leiden Early Arthritis Clinic Recruited from 1993 to 2006	Patients meeting the 1987 ACR criteria and symptom duration of ≤ 2 years

continued

TABLE 2 Data sources used in the development and external validation of the included risk prediction models (*continued*)

Name of clinical prediction model/external validation	Name and study design of data source	Setting (number of centres) and period of data collection	Key eligibility criteria
External validation studies			
De Cock[80]	Part of observational cohort (Verschueren *et al*. 2008[81])	Department of Rheumatology at University Hospitals of Leuven, Leuven, Belgium Enrolled from 2001 to 2007	Consecutive DMARD-naive early RA patients. Patients with radiographs of hands and feet at baseline, year 1 and year 2 included in study Patients in parallel RCTs excluded
Granger[82]	ESPOIR cohort	France (14 regional centres) Recruited from 2002 to 2005	Aged 18–70 years, with two or more swollen joints for > 6 weeks and < 6 months, not taking any DMARDs/steroids except for < 2 weeks before entry. Patients with RA diagnosis from rheumatologist and initiation of first cDMARD
Hambardzumyan[83]	SWEFOT RCT[90]	15 centres, Sweden Patients screened for inclusion from 2002 to 2005	Aged > 18 years, DMARD naive, early RA meeting the 1987 revised ACR criteria, with a symptom duration of < 1 year
Heimans[84]	IMPROVED (Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritis Disease) randomised trial	Multicentre trial; 12 hospitals in the Netherlands Recruited from 2007 to 2010	Patients with early RA (ACR/EULAR 2010 criteria, a symptom duration of ≤ 2 years) and UA initially treated with MTX and prednisone
Markusse[85]	Behandelings Strategie (BeSt) RCT[89]	18 peripheral and two university hospitals in the western Netherlands Patients recruited from 2000 to 2002	As for BeSt[89]

ATTRACT, anti-TNF trial in rheumatoid arthritis with concomitant therapy; DMARD, disease-modifying antirheumatic drug; HIV, human immunodeficiency virus; IQR, interquartile range; NR, not reported; TB, tuberculosis; UA, undifferentiated arthritis; VAS, visual analogue scale.

used to build models by Degboé *et al.*[66] and Fautrel *et al.*[69] Combe *et al.* developed models for the prediction of radiographic damage/progression (Combe A)[62] and HAQ score (Combe B)[63] in French cohort data. The Graell[71] and Sanmartí[75] clinical prediction model development studies used the same Spanish cohort data source. The models by Bansback *et al.*,[58] Berglin *et al.*,[59] Brennan *et al.*,[60] Centola *et al.*,[61] de Punder *et al.*,[64] Bombardier *et al.*[57] (SONORA), Dixey *et al.*,[68] Forslind *et al.*,[70] Houseman *et al.*[72] and Syversen *et al.*[76] were developed in cohort study data sets.

The five included external validation studies were also performed in appropriate data sources, being either intervention trials {i.e. Hambardzumyan *et al.*[83] (SWEFOT), Heimans *et al.*[84] [Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritis Disease (IMPROVED)], Markusse *et al.*[85] (BeSt)} or cohort study data [i.e. De Cock *et al.*[80] (Verschueren cohort), Granger *et al.*[82] (ESPOIR)].

Description of population characteristics

As outlined in *Table 3*, the majority of clinical prediction models were developed in populations that had satisfied the 1987 ACR criteria for the diagnosis of RA (i.e. ASPIRE,[78] Bansback *et al.*,[58] Berglin *et al.*,[59] BeSt,[79] Brennan *et al.*,[60] Centola *et al.*,[61] Combe (A),[62] Combe (B),[63] de Punder *et al.*,[64] de Vries-Bouwstra *et al.*,[65] Dixey *et al.*,[68] Dirven *et al.*,[67] Forslind *et al.*,[70] Graell *et al.*,[71] Houseman *et al.*,[72] Sanmartí *et al.*,[75] SWEFOT,[73] Syversen *et al.*[76] and van Steenbergen *et al.*[77]). Degboé *et al.*[66] used the 2010 ACR/EULAR criteria in their diagnosis of patients, whereas in the ESPOIR model data source, patients had received a RA diagnosis from their rheumatologist (and the proportion of patients meeting the ACR/EULAR 2010 criteria was reported). The RA diagnosis method used by Drossaers-Bakker *et al.*[56] was not specified. However, all patients were described as having RA, and two other included studies (i.e. de Vries-Bouwstra *et al.*[65] and van Steenbergen *et al.*[77]), which were also developed using data from the Leiden Early Arthritis Clinic, both had used the 1987 ACR criteria (and, therefore, the review group has assumed a similar use of the 1987 ACR criteria by Drossaers-Bakker *et al.*[56]). The amount of information available in the conference abstract by Bombardier *et al.*[57] describing the development of the SONORA clinical prediction model was limited. It was stated that patients included in the SONORA study were diagnosed with RA by a rheumatologist. The populations used in the external validation studies by Hambardzumyan *et al.*[83] and Markusse *et al.*[85] were diagnosed with RA according to the 1987 revised ACR criteria. The patients of the ESPOIR cohort, included in the Granger *et al.*[82] external validation study, were diagnosed with RA by their rheumatologist (and the proportion meeting the ACR/EULAR 2010 criteria was reported). Heimans *et al.*[84] reported that the ACR/EULAR 2010 criteria were used for the diagnosis of RA in the mixed RA/undifferentiated arthritis population used for their external validation study.[84] In the De Cock *et al.*[80] external validation study, all patients (in the Verschueren cohort) were described as being newly diagnosed with early RA.

As stated in *Study selection*, early RA was defined in conjunction with clinical experts as being within 2 years of the onset of symptoms. Included studies reported either the duration of symptoms or the duration of disease at baseline (with disease duration at baseline considered by the review team to be equivalent to symptom duration in the absence of further information). The studies set an upper threshold of symptom/disease duration for study eligibility and/or reported the median/mean symptom/disease duration at baseline, as presented in *Table 3*. Compared across studies, the baseline median/mean symptom/disease duration for included populations was typically approximately 5–6 months. The ESPOIR,[69] Combe (A)[62] and Combe (B)[63] models were derived from patients with earlier RA (mean duration of disease of 15 weeks, 3.3 months and 3.6 months, respectively). The populations in the models by Drossaers-Bakker *et al.*[56] (median symptom duration of 1 year) and Syversen *et al.*[76] (mean disease duration of 2.3 years) had disease of a longer duration. It is noted that the population used to develop the Syversen *et al.*[76] clinical prediction model was outside the 2-year limit used to define early RA. However, this study was eligible for inclusion because it was externally validated in a population that did meet the inclusion criteria (i.e. De Cock *et al.*[80]). The populations in the data sources used for the six included external validation studies were all of $\leq$ 2-year symptom/disease duration at baseline.

TABLE 3 Key population characteristics of the included risk prediction model development and external validation studies

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
Clinical prediction model development studies				
ASPIRE[78]	Satisfied the 1987 revised ACR criteria	Persistent synovitis for 3 months to 3 years Median disease duration = 0.6 years (IQR 0.4–1.1 years)	DAS28 NR	MTX-naive patients (three or fewer pre-study doses of MTX permitted) randomised to receive MTX monotherapy or MTX in combination with 3 or 6 mg/kg of infliximab through 46 weeks. IFX and MTX groups were combined in each study
Bansback[58]	Patients meeting the 1987 revised ACR criteria for RA included in the main analysis. Patients not meeting the 1987 ACR criteria followed and considered in the subgroup analysis	Patients seen within 2 years of initial symptoms The median duration of symptoms (months) reported for patients with none/mild and moderate/severe functional impairment at 5 years was: Mild group = 6 months (IQR 4–11 months) Severe group = 6 months (IQR 4–12 months)	The median DAS28 reported for patients with none/mild and moderate/severe functional impairment at 5 years was: Mild group = 5.4 (IQR 3.5–7.9) Severe = 6.2 (IQR 3.6–8.1)	DMARDs used based on physician preference using standard practice of the late 1980s/1990s (i.e. sequential monotherapy and 'step-up' combination treatment for more severe RA). A total of 801 patients (81%) received ≥ 1 DMARDs starting at a median of 2 months (68% by 3 months and 87% by 12 months). The remaining 19% of patients received NSAIDs and/or low-dose steroids. 54% of patients received SSZ, 18% received MTX, 13% received intramuscular gold, 9% received D-penicillamine, 4% received antimalarials and 2% received unspecified treatments. A total of 55% of DMARD-treated patients received ≥ 1 drugs. A total of 17% ($n = 164$) received steroids at ≥ 7.5 mg daily for ≥ 12 months
Berglin[59]	Patients met the 1987 revised ACR classification criteria for RA	Baseline median time after the onset of symptoms = 7.0 months (IQR 5.0–9.0 months)	NR	During the study, 92% of patients were treated with DMARDs for > 6 months (68% received MTX, 30% received SSZ, 14% received oral/parenteral gold, 12% received antimalarials, 0.7% received anti-TNF agents, 12% received other unspecified DMARDs and 30% received combination therapy). A total of 48% of patients received low-dose prednisolone (at ≤ 10 mg/day) for > 6 months during study

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
BeSt[79]	The 1987 revised ACR criteria	Symptom duration of ≤ 2 years Baseline symptom duration, median number of weeks: MTX monotherapy = 25 weeks (IQR 14–55 weeks) Combination with prednisone = 24 weeks (IQR 15–56 weeks) Combination with IFX = 22 weeks (IQR 13–44 weeks)	NR A DAS of 4.3–4.5 across groups	All patients were DMARD naive and met the 1987 ACR criteria for RA. Patients receiving dynamic treatment strategies (aimed at a low level of disease activity, shown by a DAS of ≤ 2.4). Group 1 ($n = 126$) and group 2 ($n = 121$) patients began initial MTX monotherapy which could be switched/extended with other DMARDs. Group 3 ($n = 133$) patients began combination MTX, SSZ, HCQ and tapered high-dose prednisone. Group 4 ($n = 128$) patients began a combination of MTX and IFX. Treatment was adjusted every 3 months in accordance with the fixed protocol with the aim of achieving a DAS of ≤ 2.4. Groups 1 and 2 were combined for the current analysis. Used data from patients randomised to initial monotherapy or combination therapy
Brennan[60]	Satisfied any subset of the American Rheumatism Association 1987 revised RA criteria	Patients were recruited within 180 days of the onset of symptoms Baseline disease duration [(days) length of time between patient-reported onset of symptoms and first examination by a metrologist from the study]: 0–90 days, $n = 91$ (52%) 91–180 days, $n = 84$ (48%)	NR	83 out of 175 patients (47%) were treated with second-line drugs at baseline (SSZ, 66/83 patients) Treated with steroids at baseline, $n = 35$ (20%)

continued

TABLE 3 Key population characteristics of the included risk prediction model development and external validation studies (*continued*)

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
Centola[61]	Feasibility studies (stage 2 I–V): all patients met four or more of the seven 1987 revised ACR criteria for RA Algorithm training study (stage 3): all patients met four or more of the seven 1987 revised ACR criteria for RA	Feasibility studies (stage 2 I–V): NR Algorithm training study (stage 3): NR	Feasibility studies (stage 2 I–V): DAS28-CRP median = 3.8 (IQR 2.7–5.0) to 5.8 (IQR 4.7–6.5) Algorithm training study (stage 3): DAS28-CRP median = 3.8 (IQR1.6–6.4)	Feasibility studies (stage 2 I–V): MTX, 48–64%; non-biologic DMARDs, 64–81%; biologics, 43–65%; and corticosteroids, 24–33% Algorithm training study (stage 3) NR
Combe (A)[62]	Patients met the ACR criteria for RA	Disease duration of < 1 year Mean duration of disease at baseline = 3.3 months (SD 2.6 months)	NR Mean DAS: 4.1 (SD 0.8)	Patients were DMARD naive at entry, treated with DMARDs (typically MTX or SSZ, modifiable based on efficacy/side effects). During 3-year study, mean of 1.7 DMARDs used (range 1–5; MTX, *n* = 166 patients; SSZ, *n* = 146 patients; gold, *n* = 32 patients; HCQ, *n* = 20 patients; D-penicillamine, *n* = 13 patients; and CsA, *n* = 1 patients). A total of 63 patients received low-dose prednisone (5–15 mg/day) on more than one occasion during follow-up
Combe (B)[63]	Patients met the ACR criteria for RA	Disease duration of < 1 year Mean duration of disease at baseline = 3.6 months (SD 2.6 months)	NR Mean DAS: 4.1 (SD 0.8)	Patients were DMARD naive at entry, treated with DMARDs (typically MTX or SSZ, modifiable based on efficacy/side effects). During the 5-year study, a mean of 1.95 DMARDs was used (range 1–5; MTX, *n* = 175 patients; SSZ, *n* = 147 patients; gold, *n* = 41 patients; HCQ, *n* = 25 patients; D-penicillamine, *n* = 14 patients; and CsA, *n* = 1 patient). A total of 63 patients received low-dose prednisone (5–15 mg/day) on more than one occasion during follow-up

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
de Punder[64]	Satisfied the 1987 ACR criteria for RA	Disease duration of ≤ 1 year	Mean baseline DAS28 reported for groups with: 1. joint damage progression [DAS28 = 5.5 (SD 1.3)] 2. no joint damage progression [DAS28 = 4.9 (1.4)]	Joint damage progression group: • Combination of DMARDs (unspecified), *n* = 37 (21%) • Monotherapy DMARDs (unspecified), *n* = 132 (75%) • Oral prednisone, *n* = 107 (61%) No joint damage progression group: • Combination DMARDs (unspecified), *n* = 51 (20%) • Monotherapy DMARDs (unspecified), *n* = 181 (72%) • Oral prednisone, *n* = 152 (61%)
de Vries-Bouwstra[65]	Definite RA in accordance with the 1987 revised ACR criteria, but without the criterion that symptoms must be of 6 weeks' duration and observed by a physician	Duration of symptoms: < 2 years Median symptom duration at first visit = 22 weeks (IQR 11–45 weeks)	NR	A total of 85% of included patients who received DMARDs during the first year after diagnosis (starting with HCQ for 40% of patients, SSZ for 30% of patients or unspecified other drugs for 30% of patients). A total of 14 patients (9.2%) received combination DMARDs in the first year, nine patients received a combination of antimalarial drugs with other DMARDs (*n* = 3 patients received antimalarial drugs and MTX; *n* = 5 patients received antimalarial drugs and ciclosporin; and *n* = 1 patient received antimalarial drugs and experimental peptide vaccination strategy). Other combinations: SSZ and low-dose prednisone (*n* = 2); MTX and low-dose prednisone (*n* = 2); and SSZ and interferon-beta (*n* = 1). DMARD combination commenced after a mean of 24 weeks after presentation. No patient was treated with combination drugs directly after presentation

continued

TABLE 3 Key population characteristics of the included risk prediction model development and external validation studies (*continued*)

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
Degboé[66]	RA according to the 2010 ACR/EULAR criteria	Two or more swollen joints for > 6 weeks and < 6 months Median disease duration = 5.0 months (IQR 3.1–7.4 months)	NR	Baseline treatment: steroids, $n = 71$ patients (12.5%) Year 1 treatment: steroids, $n = 259$ patients (45.8%) Any DMARDs, $n = 436$ patients (82.4). Biologic DMARDs, $n = 40$ patients (7.1%)
Dirven[67]	RA according to the 1987 revised ACR criteria	Median symptom duration (weeks) at baseline: MTX monotherapy group = 25 weeks (IQR 14–55 weeks) Combination + prednisone = 23 weeks (IQR 15–53 weeks) Combination + IFX = 23 weeks (IQR 13–46 weeks)	Mean DAS at baseline: MTX monotherapy group = 4.5 (SD 0.9) Combination + prednisone = 4.4 (SD 0.9) Combination + IFX = 4.3 (SD 0.9)	For analysis, strategy groups 1 and 2 combined as patients achieved a HAQ score at 3 months on the same initial treatment, i.e. MTX monotherapy. In strategy 3, patients started on combination MTX, SSZ and tapered high-dose prednisone. In strategy 4, patients started on a combination of MTX and IFX
Dixey[68]	RA according to the 1987 revised ACR criteria	Duration of symptoms for ≤ 2 years Median duration of RA symptoms prior to presentation to the rheumatologist and study entry was 6 months (4–11 months)	NR	DMARD selected according to physician preference. A total of 80% of patients received at least one DMARD at a median of 7 weeks from first presentation to a rheumatology clinic. First DMARD: • SSZ, 73% • Intramuscular gold, 10% • D-penicillamine, 7% • Oral gold, 3% • Antimalarials, 3% • MTX, 3% • Various others (azathioprine, ciclosporin, cyclophosphamide) A total of 16% of patients used steroids at a dose of ≥ 7.5 mg daily for ≥ 12 months

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
Drossaers-Bakker[56]	NR (all RA), but de Vries-Bouwstra *et al.* (2006)[65] and van Steenbergen *et al.* (2015)[77] samples from the Leiden Early Arthritis Clinic both used the 1987 revised ACR criteria (therefore assumed a similar use of the 1987 revised ACR criteria)	Symptoms of < 5 years' duration (median 1 year)	Median baseline DAS = 2.8 (IQR NR)	NR
ESPOIR[69]	RA diagnosis according to the rheumatologist; *n* = 316 patients (85.4%) met the ACR/EULAR criteria at baseline	Early arthritis for < 6 months, two or more swollen joints for > 6 weeks and < 6 months Mean disease duration of 15.2 weeks (SD 15.4 weeks)	Mean DAS28 = 5.4 (SD 1.2)	One hundred per cent of patients received MTX or LEF as a first-line agent Treatment based on usual care by rheumatologist. A total of 370 patients started MTX (*n* = 335, mean dose of 17.5 mg/week) or LEF (*n* = 35, mean dose of 20 mg/week). A total of 302 patients still receiving MTX at 1 year, 19 patients switched to another cDMARD and 11 patients switched to a bDMARD. Two patients receiving LEF switched to a bDMARD at 1 year
Forslind[70]	RA satisfying the 1987 revised ACR criteria	Disease duration of ≤ 1 year Median disease duration at baseline = 6 months (IQR 4–8 months)	Median DAS28 at baseline = 5.10 (IQR 4.22–5.85)	Patients were DMARD naive and corticosteroid naive at entry. At baseline, patients were given: MTX, 36%; SSZ, 51%; other unspecified DMARDs, 13%; and MTX and SSZ, *n* = 1. At study end, 254 patients received DMARD treatment (MTX, 49%; SSZ, 22%; other unspecified DMARD, 19%; 10% combination therapy). At the start, 167 patients received low-dose prednisolone (mean) at a daily dose of 8.30 mg (SD 2.45 mg) and by study end, 155 patients were receiving prednisolone at a dose of 5.90 mg/day (SD 2.70 mg/day)

continued

TABLE 3 Key population characteristics of the included risk prediction model development and external validation studies (*continued*)

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
Graell[71]	Patients met the 1987 revised ACR criteria	Symptoms for < 24 months, Baseline mean disease duration = 10 months (SD 6.7 months)	Mean DAS28 5.66 (SD 0.91)	Patients treated with therapeutic protocol with the early use of DMARDs using a step-up approach. 50 mg/week of intramuscular sodium aurothiomalate prescribed as first-choice DMARD plus 4 mg/day of methylprednisolone. NSAIDs and intra-articular steroids were given at clinical discretion. Introduction of MTX at a dose of 7.5–30 mg if adverse events/lack of efficacy at 6 months (or according to clinical discretion for a high level of disease activity before 6 months). ACR50 responders at 6 months received gold salts every 2 or 3 weeks. ACR20 criteria responders (but not ACR50 criteria responders) at 6 months received a combination of sodium aurothiomalate and MTX. Tapering of oral steroids was done according to clinical judgement. After 1 year, patients were treated using an aggressive approach informed by clinical judgement (with initiation of other DMARDs/bDMARDs when required)
Houseman[72]	Satisfied the 1987 revised ACR criteria for RA	Onset of persistent symptoms of < 2 years before entry Median disease duration: • Low-progressors group = 260 (IQR 169–412) days • High-progressors group = 242 (IQR 146–384)	Median baseline DAS28: • Low-progressors group = 5.1 (IQR 4.0–6.1) • High-progressors group = 6.2 (IQR 4.8–6.8)	Treatment according to local practice with sequential DMARD monotherapy or combination therapy. Five patients subsequently received anti-TNF therapy
Sanmartí[75]	Patients met the 1987 revised ACR criteria	Disease duration of < 2 years Baseline mean disease duration = 10 months (SD 6.7 months)	Mean DAS28 of 5.7 (SD 0.9); 75.7% of patients had a DAS28 of > 5.1	Patients treated with therapeutic protocol (as for Graell *et al.*[71]) of gold salts and MTX in a step-up approach plus methylprednisolone (4 mg/day)

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
SONORA[57]	Patients diagnosed with RA by a rheumatologist (method NR)	Symptom duration of ≥ 3 and ≤ 12 months Mean disease duration 170 days (SD 180 days)	NR	NR
SWEFOT[73]	RA according to the 1987 revised ACR criteria	Symptom duration of < 1 year Median symptom duration = 5 months (IQR 4–8 months)	Median baseline DAS28 = 5.8 (IQR 5.0–6.4)	Baseline concurrent prednisolone, $n = 42$ patients (14%) Baseline concurrent NSAIDs, $n = 192$ patients (62%) MTX monotherapy, combination with IFX, combination with SSZ and HCQ
Syversen[76]	Clinical diagnosis of RA according to the 1987 ACR criteria	Mean disease duration at baseline = 2.3 years (SD 1.2 years)	DAS28 NR	Patients treated according to rheumatologist preference Baseline (10-year follow-up) treatments: • DMARDs, 52.1% (48%) • NSAIDs, 52% (44%) • Prednisolone, 25% (36%) • Anti-TNFs, 0% (12%) A total of 14.1% of patients received no DMARDs or anti-TNFs during the study
van Steenbergen[77]	Patients meeting the 1987 ACR criteria	Symptom duration of ≤ 2 years	NR	Initial treatment differed based on the inclusion time period: • 1993–5, initial NSAIDs • 1996–8, initial HCQ or SSZ • Since 1999, initial MTX

continued

TABLE 3 Key population characteristics of the included risk prediction model development and external validation studies (*continued*)

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
External validation studies				
De Cock[80]	All newly diagnosed early RA patients (method NR)	Mean symptom duration: 8 months (SD 7 months) Mean disease duration: 1 month (SD 1 month)	Mean DAS28-CR: 4.91 (SD1.22)	ICTS ($n = 32$ patients) or IMT ($n = 42$ patients) received based on patient RA severity according to rheumatologist opinion. Evaluated at least every 4 months
Granger[82]	Patients with RA diagnosis from their rheumatologist ($n = 316$, 85.4% met the 2010 ACR/EULAR criteria)	Disease duration of 15.2 weeks (SD 8.2 weeks)	DAS28: 5.3 (SD 1.2)	ESPOIR treatment strategies were not protocol based. Included patients in this study received MTX or LEF for at least 3 months within the first year of follow-up. Duration of DMARD treatment during the first year of 9.06 months (SD 3.07 months), 26% of patients received concomitant glucocorticoids. Some patients received an 'insufficient dosage' of another treatment (cDMARD or bDMARD); this not considered in the analysis
Hambardzumyan[83]	RA in accordance with the 1987 revised ACR criteria	Mean symptom duration: 6.2 months (SD 4.57 months)	Baseline mean DAS28-ESR: 5.7 (SD 1.01) Baseline mean DAS28-CRP: 6.5 (SD 1.22)	As for the SWEFOT RCT

Name of clinical prediction model/external validation study	Diagnosis (and proportion) of RA	Duration of symptoms/disease at baseline	DAS28 at baseline	Treatment
Heimans[91]	Mixed RA/UA population (80.3% of the population for the matrix model had RA) [Patients with early RA (ACR/EULAR 2010 criteria)]	Symptom duration of ≤ 2 years (Heimans *et al.* 2014) Median symptom duration: 18 weeks (IQR 9–34 weeks)	DAS28 NR Mean baseline DAS: 3.34 (SD 0.9)	IMPROVED study patients initially treated with MTX at a dose of 25 mg/week and prednisone at a dose of 60 mg/day tapered to 7.5 mg/day in 7 weeks. Medication tapered in patients reaching early remission (a DAS of < 1.6 after 4 months). Patients not in early remission after 4 months randomised to either MTX at a dose of 25 mg/week and HCQ at a dose of 400 mg/day and SSZ at a dose of 2000 mg/day and prednisone at a dose of 7.5 mg/day (study arm 1) or to MTX at a dose of 25 mg/week and ADA at a dose of 40 mg/2 weeks (study arm 2). During follow-up, medication was increased or switched in the case of no remission and tapered or stopped in the case of remission
Markusse[85]	1987 revised ACR criteria	NR, but disease duration of ≤ 2 years in BeSt RCT	Mean baseline DAS28 ranged from 5.82 (SD 1.03) to 5.98 (SD 1.00)	As for BeSt

CsA, ciclosporin A; DMARD, disease-modifying antirheumatic drug; ICTS, initial DMARD combination therapy with steroids; IMT, DMARD monotherapy; IQR, interquartile range; NR, not reported; UA, undifferentiated arthritis.

The DAS28 disease severity score at baseline was tabulated when available. A DAS28 of ≥ 5.1 is classed as severe disease, whereas a DAS28 of 3.2–5.1 is regarded as moderate disease severity.[19] Unfortunately, the DAS28 at baseline was not available for the majority of studies. Five clinical prediction models (i.e. ESPOIR,[69] Forslind *et al.*,[70] Graell *et al.*,[71] Sanmartí *et al.*[75] and SWEFOT[73]) were developed in populations that were defined as having severe disease activity based on the DAS28. Two external validation studies were performed in populations with severe DAS28 (i.e. Granger *et al.*[82] and Hambardzumyan *et al.*[83]). In some studies, the DAS28 at baseline was reported only for subgroups (rather than for the total population), but indicated a severe DAS28. The cohort used in the De Cock *et al.*[80] external validation was borderline between the moderate and severe DAS28 categories [mean DAS28-CRP of 4.91 (SD 1.22)].[80] Therefore, unfortunately, sufficient data were not available to evaluate the performance of predictors across moderate and severe DAS28 populations.

The treatment histories and concurrent treatments in included studies are described in *Table 3*. Additional population characteristics at baseline are presented in *Appendix 7*, *Table 30*.

The data sources and participant selection in the included studies were assessed using domain 1 of the PROBAST tool[49] (see *Appendix 6*).

Appropriate data sources were considered to have been used for all model development and external validation studies. Inclusions and exclusions of participants were considered by the review authors to be acceptable overall. However, it was noted that the Drossaers-Bakker model[56] included only female participants, which may affect the generalisability of the model. As explained previously, the Syversen model[76] was developed in a population with a longer mean disease duration [mean 2.3 years (SD 1.2 years)]. Although the Syversen model[76] has been externally validated in a relevant population, this may affect the performance of the model.

It was stated in the final protocol that, for review 1, patients should have been diagnosed with early RA according to established criteria. The methods used for RA diagnosis in included studies are presented in *Table 3*. The lack of clarity around the method of RA diagnosis used in the populations in the Drossaers-Bakker[56] and SONORA[57] clinical prediction models and the De Cock external validation study[80] may contribute to a potential source of bias. The De Cock external validation study[80] was based on a cohort recruited at the University of Leuven, Belgium. The original report for this study cohort described patients as being 'newly diagnosed with RA.' Although the specific method used for diagnosis was not reported, the entire cohort was described as having a diagnosis of RA and the duration of symptoms meets our definition of early RA. Therefore, in light of the fact that the De Cock external validation study[80] presents key informative evidence comparing the performance of multiple clinical prediction models and is described as being based on an early RA cohort, this study has been included.[80]

Three model development studies were rated as having an unclear risk of participant selection bias on PROBAST domain 1 [i.e. Drossaers-Bakker *et al.*,[56] Bombardier *et al.* (SONORA)[57] and Syversen *et al.*[76]]. All other remaining model development studies were rated as being at a low risk of participant selection bias. Two external validation studies were rated as having an unclear risk of bias for participant selection (i.e. De Cock *et al.*[80] and Heimans *et al.*[84]). All other external validation studies were categorised as having a low risk of bias for participant selection.

Description of predictors

The candidate predictors considered in the development of clinical prediction models are presented in *Table 4*. The candidate predictors were interpreted by the review team to be all predictors considered in the model development process (and were not limited to those included in the multivariable analysis) in line with the definition applied in CHARMS (i.e. Moons *et al.*[48]).

TABLE 4 Characteristics of the candidate predictors studied in the included clinical prediction model development studies

Name of the clinical prediction model development study	Definition and measurement of candidate predictors	Timing of measurement
ASPIRE[78]	TJC, SJC, ESR (Westergren method), CRP level (nephelometry), IgM RF and radiographs of hands and feet. Association tested between 'all available baseline variables' from the ASPIRE data set and radiographic progression	Baseline
Bansback[58]	Model development involved the removal of predictors from the full 35-predictor model. Nineteen individual candidate predictors reported: sex, age at onset, months of RA symptoms prior to diagnosis, RF, presence of nodules, Carstairs deprivation index, ACR criteria, number of DMARDs used in the first year, functional grades I–IV, morning stiffness (hours), SJC, TJC, grip strength (0–300 mm), HAQ score, pain score (VAS 0–100), haemoglobin level, ESR, DAS28 and radiographic damage, scored using the Larsen Damage and Erosion Scores	Baseline and 1 year
Berglin[59]	NR, but the multivariable analysis included anti-CCP, IgG, IgM, IgA RF by ELISA, SE via HLA-DRB1 genotyping, ESR (mm/hour), SJC28, Larsen score, therapeutic EULAR response at 6 months	Baseline and therapeutic response at 6 months
BeSt[79]	Age, sex, BMI, symptom duration, smoking, SJC, TJC, DAS, CRP (mg/l), ESR (mm/hour), HAQ score, total SHS, erosion score, IgM RF positivity (measured in participating hospitals according to cut-off point of each laboratory) and ACPA positivity (EuroDiagnostica, Arnhem, the Netherlands and Axis-Shield Diagnostics, Dundee, UK)	Baseline
Brennan[60]	A total of 11 individual candidate predictors reported as being measured at baseline (assumed all were entered into modelling): RF titre (from tube latex test, 1 : 80 cut-off point for positive result), swelling of specific joint areas, number of swollen joints, duration of morning stiffness, presence of rheumatoid nodules, disability score, age, sex, disease duration (length of time between symptom onset and first presentation to register metrologist: < 90 days or 90–180 days), time between onset of disease and radiography and HAQ score	Baseline
Centola[61]	Candidate predictors selected using a multistage approach. A total of 130 candidate biomarkers were tested in feasibility studies and 25 were tested in algorithm development, training and selection	Unclear (assumed baseline for subset of patients)
Combe (A)[62]	Age, sex, BMI, disease duration, duration of morning stiffness, patient VAS pain, SJC, TJC, Ritchie Articular Index, DAS, presence/absence of nodules and extra-articular manifestations, HAQ score, ESR, CRP level, IgA and IgM RF positivity by enzyme-linked immunosorbent assay (ELISA), antikeratin anti-body positivity, antiperinuclear anti-body positivity, antiRA33 anti-body positivity, antiheat shock protein positivity, anticalpastatin anti-body positivity, YKL-40 positivity, antinuclear anti-body positivity, HLA-DRB1 and DQB1 genotyping, SHS	Baseline
Combe (B)[63]	Age, sex, BMI, disease duration, duration of morning stiffness, patient VAS pain, swollen and tender joint counts, Ritchie Articular Index, DAS, presence/absence of nodules and extra-articular manifestations, HAQ score, ESR, CRP level, IgA and IgM RF positivity by ELISA, antikeratin anti-body positivity, antiperinuclear anti-body positivity, antiRA33 anti-body positivity, antiheat shock protein-90 positivity, anticalpastatin anti-body positivity, YKL-40 positivity, antinuclear anti-body positivity, HLA-DRB1 and DQB1 genotyping and radiographic score	Baseline

continued

TABLE 4 Characteristics of the candidate predictors studied in the included clinical prediction model development studies (*continued*)

Name of the clinical prediction model development study	Definition and measurement of candidate predictors	Timing of measurement
de Punder[64]	Anti-CCP and/or RF (0, 1 or 2 positive) (positive anti-CCP level of > 25 U/ml, ELISA immunoscan RA mark 2, > 10 U/l for frozen samples, EliA™ CCP (Thermo Fisher Scientific, Waltham, MA, USA; positive RF of > 10 U/ml), SE (positive/negative), smoking status (ever or never), ESR (< 25 , 25–50 or > 50 mm/hour), CRP level (≤ 5, 6–10, ≥ 11 mg/dl), SJC28 (0–5, 6–10, 11–15, > 15), TJC28 (0–5, 6–10, 11–15, > 15), VAS general health (0–29, 30–60, 61–100), VAS pain (0–29, 30–60, 61–100), erosions (0, 1–5, 6–10, > 10 Ratingen points), DAS28 (≤ 3.2, 3.3–5.1, ≥ 5.2), age and sex	Baseline
de Vries-Bouwstra[65]	Age (continuous), sex, duration of symptoms at presentation (> 6 weeks or ≤ 6 weeks), duration of morning stiffness (continuous), patient's global assessment of disease activity (continuous), HAQ score (continuous), total SJC [maximum 22 (continuous)], Ritchie Articular Index score (continuous), bilateral compression pain in metatarsophalangeals (categorical), IgM RF positivity (≥ 5 U) by ELISA (categorical), ESR (continuous), SE hetero- or homozygosity (categorical), presence of erosions on radiographs (categorical), SHS (continuous) and DMARD therapy received	Baseline
Degboé[66]	Anti-CCPs [anti-CCP2 (DiaSorin, Saluggia, Italy], anti-mutated citrullinated vimentin [positivity of > 20 UA/ml (Orgentec, Mainz, Germany)], anticitrullinated fibrinogen (positivity of > 0.056 AU, in-house ELISA). Categorised as negative, low titre, high titre, IgM RF [(Menarini Diagnostics, Winnersh, UK) positivity of > 9 UI/ml], presence of HLA-DRB1 SE (typing and subtyping using PCR), ESR, CRP level, age, sex, duration of disease course before inclusion, smoking consumption, clinical centre, presence of erosions at baseline and treatment (use of steroids, synthetic or biologic DMARDs within the first year tested in the model)	Baseline
Dirven[67]	Age, sex, symptom duration, DAS, HAQ, pain, Ritchie Articular Index, SJC, TJC, treatment group, presence of RF, anti-CCP, radiological damage (total SHS, erosion score, narrowing score, erosions), SE, smoking status, VAS disease activity, VAS pain, VAS morning stiffness, VAS global health, BMI, CRP level and ESR	Baseline
Dixey[68]	Larsen erosion score, RF, ESR, haemoglobin level, nodules, SJC, grip strength, duration of symptoms, presence of HLA-DR SE, HAQ, DAS. All continuous variables were categorised into quartiles	Baseline and 1 year
Drossaers-Bakker[56]	Disease duration, RF, HLA-DQ and HLA-DR SEs, RA protected, percentage agalactosyl IgG, SJC, Ritchie score, presence of erosions and HAQ score	Baseline
ESPOIR[69]	Age, sex, SJC28 (< 14, 14–20 or ≥ 20), TJC28, ESR, CRP (mg/l, < 4, 4–35 or ≥ 35), elevated ESR or CRP level, DAS28-ESR, ACPA positivity, RF positivity, ACPA or RF positivity, HAQ score, typical RA erosion, disease duration, prednisone at a dose of ≥ 7.5 mg/g, delay before first DMARD initiation for ≥ 6 months after the onset of RA, satisfaction of the 2010 ACR/EULAR criteria. Combe 2007 ESPOIR description: clinical and biological variables recorded at baseline and each visit. Baseline CRP level (number of < 10 mg/l), IgM and IgA RF [ELISA (Menarini, Rungis, France), positive at > 9 U/ml], anti-CCP2 anti-bodies [ELISA (DiaSorin, Antony, France), positive at > 5 U/ml] measured for all patients using the same method in a central laboratory	Baseline

TABLE 4 Characteristics of the candidate predictors studied in the included clinical prediction model development studies (*continued*)

Name of the clinical prediction model development study	Definition and measurement of candidate predictors	Timing of measurement
Forslind[70]	Anti-CCP1 [ELISA (EuroDiagnostica, Malmö, Sweden)], positive result titre of ≥ 25 U/ml), RF [Serodia agglutination test (Fujirebio Inc., Tokyo, Japan)], positive result titre of 20 IU/ml), HLA-DRB104 genotyping, DAS28, ESR (mm/hour), CRP (mg/l), VAS global health, VAS pain, HAQ score and Larsen score	Baseline
Graell[71]	Sex, age, disease duration, marital status (widowed), handworkers, education, active work, HLA-DRB104, SE, RF (> 25 U/l), anti-CCP (> 50 U/l), ESR (mm/hour), CRP (mg/dl), haemoglobin level, TJC28, SJC28, patient's global assessment, physician's global assessment, VAS pain, DAS28, a DAS28 of > 5.1, MHAQ and Larsen score	Baseline
Houseman[72]	Anti-CCP positivity [titre of > 6 U/ml (Axis-Shield Diagnostics, Dundee, UK)], RF (> 40 U/ml), elevated MMP-3 levels (i.e. > 85.79 ng/ml), C-telopeptide of type II collagen level (> 20 µg/mmol), cartilage oligomeric matrix protein level (> 11.20 U/l), tissue inhibitor of metalloproteinase 1 level(> 688.68 ng/ml,) ESR (> 20 mm/hour), CRP level (> 5 mg/l), radiographic damage (i.e. a SHS of > 7) and a physician's global assessment on the VAS (> 49.00 mm)	Baseline, anti-CCP taken at the 8.2-year follow-up
Sanmartí[75]	NR, but univariable analysis reported to include significant factors: haemoglobin level, ESR, sex, SE, SE homozygosity, HLA-DRB1*04 genotype, anti-CCP, RF and MHAQ	Baseline
SONORA[57]	Limited reporting of candidate predictors	Baseline
SWEFOT[73]	Sex, age, symptom duration, anti-CCP positivity [Immunoscan-RA mark 2 (ELISA test, EuroDiagnostica, Malmö, Sweden)], RF positivity, (determined using routine methods), RF and/or anti-CCP positivity, smoking status (current, past or never), radiographic erosions, concurrent prednisolone use, DAS28 (per unit increase), SJC (< 10, 10–17 or > 17), TJC (per increase of 10), CRP level (< 10 mg/dl, 10–35 mg/dl, > 35 mg/dl), ESR (< 21 mm/hour, 21–50 mm/hour or > 50 mm/hour), VAS-global health (per increase of 10), HAQ score (per unit increase) and HLA-DRB1 SE	Baseline
Syversen[76]	CRP [positive at > 10 mg/l; phyCardioPhase hsCRP (Dade Behring Inc., Deerfield, IL, USA)], ESR (positive at > 20 mm/hour; Westergren method range 0–140 mm/hour), anti-CCP [negative at < 25 U/ml, 25–200 U/ml (low to moderate) or > 200 U/ml (high), as assessed via second-generation ELISA (Inova Diagnostics, San Diego, CA, USA)], IgA RF and IgM RF (positive at > 25 U/l, in-house ELISA), sex, HAQ score, age and radiographic progression rate	Baseline
van Steenbergen[77]	Age, sex, symptom duration at first visit, localisation of initial joint symptoms, SJC66, ACPA status, RF, ESR, SE, selected SNPs located in/nearby gene(s) (i.e. *CD40*, *IL-15*, *DKK-1*, *IL2RA*, *GRZB*, *IL4R*, *SPAG16*, *C5orf30*, *MMP-9*, *rs1465788* and *OPG*)	Baseline

AhFibA, anti-human citrullinated fibrinogen anti-body; anti-CCP2, anti-cyclic citrullinated peptide-2; AU, arbitrary units; *C5orf30*, chromosome 5 open reading frame 30; CCP, cyclic citrullinated peptide; *CD40*, cluster of differentiation 40; DMARD, disease-modifying antirheumatic drug; ELISA, enzyme-linked immunosorbent assay; *GRZB*, granzyme B; HLA, human leucocyte antigen; hsCRP, high-sensitivity CRP; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; *IL-15*, interleukin 15; *IL2RA*, interleukin 2 receptor alpha chain; *IL4R*, interleukin 4 receptor; MHAQ, modified Health Assessment Questionnaire; MMP-3, matrix metalloproteinase 3; *MMP-9*, matrix metalloproteinase 9; NR, not reported; *OPG*, osteoprotegerin; PCR, polymerase chain reaction; *rs*, reference SNP cluster ID; SE, shared epitope; SHS, Sharp–van der Heijde score; SJC28, 28 swollen joint count; SNP, single nucleotide polymorphism; *SPAG16*, sperm-associated antigen 16; TJC28, 28 tender joint count; VAS, visual analogue scale.

The timings of the measurement of candidate predictors in the included model development studies were noted. Measurement was at baseline for all studies, although some studies (i.e. Bansback *et al.*,[58] Berglin *et al.*,[59] Dixey *et al.*[68] and Houseman *et al.*[72]) also measured predictors at later time points. Anti-CCP positivity was measured at the extension visit (at 8.2 years of follow-up) in the Houseman *et al.* study[72] and was also included in the final clinical prediction models. The inclusion of predictors measured at substantially later time points is potentially problematic to the validity of the resulting clinical prediction model. Variables measured at later time points are problematic: they cannot be used to make predictions about outcomes in patients with newly diagnosed RA in clinical practice because the observation will not be available until after the decision has been made to treat the patient. The outcome will depend on the specific sequence of treatments administered, and such observations will bias the model relative to models that use only baseline information. None of these models has been externally validated, which highlights the difficulty in their application.

Given the incomplete reporting in the conference abstract, it was unclear which candidate predictors were considered in the SONORA model.[57]

We considered whether or not all relevant candidate predictors were analysed (i.e. whether or not all variables selected for inclusion in conjunction with clinical advisors were considered in the model development studies as candidate predictors). When selected variables of interest were not examined as candidate predictors, these studies were rated as being at an unclear risk of bias (as it was not clear what potential contribution the untested predictors may have had).

Description of outcomes

The outcomes assessed by the included studies are presented in *Table 5* for the model development studies and in *Table 6* for the external validation studies.

Among the clinical prediction model development studies, the majority assessed radiographic joint damage as an outcome. Six models were developed to predict radiographic progression [modified Sharp–van der Heijde score (SHS)] at 1 year: ASPIRE,[78] BeSt,[79] de Vries-Bouwstra,[65] Degboé,[66] ESPOIR[69] and SWEFOT.[73] The SONORA model[57] assessed radiographic progression (original Sharp score) at 1 and 2 years. Combe (A)[62] predicted radiographic score and radiographic progression (modified SHS) at 3 years. Van Steenbergen *et al.*[77] and Houseman *et al.*[72] studied radiographic progression (modified SHS) at 6 and 8.2 years, respectively. The Syversen model[76] predicted radiographic progression (modified SHS) over the longest follow-up period (i.e. 10 years). Five studies evaluated radiographic joint damage/progression, measured using the Larsen score (i.e. Brennan *et al.*[60] at 1 year; Berglin *et al.*,[59] Forslind *et al.*[70] and Sanmartí *et al.*[75] at 2 years; and Dixey *et al.*[68] at 3 years). De Punder *et al.*[64] assessed radiographic progression (according to the Ratingen score) at 3 years.

Five other clinical prediction models were designed for the prediction of other eligible outcomes. Dirven *et al.*[67] assessed short-term functional disability (HAQ score of ≥ 1) after 3 months of treatment. The outcome used in the Graell model[71] was the modified HAQ (MHAQ) at 2 years. Bansback *et al.*[58] and Combe (B)[63] both modelled the HAQ score at 5 years [with Combe (B)[63] also modelling the 3-year HAQ score]. Drossaers-Bakker *et al.*[56] included a broad range of outcomes, categorised as (1) body functions and structure (impairment), (2) activities at the individual level (disability), (3) participation in society (handicap) and (4) disease course. However, because of unclear reporting, the performance of the individual models could not be summarised, and so this study was counted as a single model in the combined total of 39 included models.

TABLE 5 Definition of the outcomes in the included model development studies

Name of clinical prediction model	Outcome category	Outcome definition and measurement	Predicted time point
ASPIRE[78]	Radiographic progression (modified SHS)[a]	Radiographs of hands and feet obtained and scored using the van der Heijde modification of the SHS. RRP was defined as a threshold change in the modified Sharp/van der Heijde (SHS) of ≥ 5 U/year	1 year
Bansback[58]	HAQ score	A HAQ score of ≥ 1.5 was defined as moderate to severe disease. Patients completed the disability index of the modified Stanford HAQ (range 0–3)	5 years
Berglin[59]	Radiographic progression (Larsen)	Radiographic progression defined as present if the difference in Larsen score at baseline and 2 years was greater than the median value. Posteroanterior radiographs of hands, wrists and feet	2 years
BeSt[79]	Radiographic progression (SHS)[a]	Radiographs of hands and feet taken at baseline and after 1 year. RRP (increase in SHS of ≥ 5 after 1 year)	1 year
Brennan[60]	Presence of radiological erosions (Larsen)	Presence of radiological erosions in hands or feet, or both, at least 12 months after the onset of symptoms. Radiographs scored using the Larsen method and patients dichotomised according to the radiographic evidence of erosions in any joints of the hands/feet (Larsen's grade ≥ 2)	1 year
Centola[61]	DAS28	Low level of disease activity/moderate to high level of disease activity (using cut-off points of DAS28-CRP of 2.67 or median DAS28-CRP)	NR
Combe (A)[62]	Radiographic score and radiographic progression (SHS)	Hand, wrist and foot radiographs taken at baseline and 3 years, scored using the SHS method. Radiographic progression defined by a change in radiographic scores that are greater than the upper boundary of 95% CI of differences (i.e. change of at least 3.2, 2.9 and 3.4 in erosions score, narrowing score and total damage score, respectively)	3 years
Combe (B)[63]	HAQ score	Functional disability according to the HAQ score (as a continuous variable)	3 and 5 years
de Punder (extended)[64]	Radiographic progression (Ratingen)	Radiographs at baseline and after 3 years of follow-up scored using the Ratingen method. Modelled change in Ratingen score between baseline and 3 years. Joint damage progression defined as the difference in ≥ 5 Ratingen points between baseline and 36 months' follow-up	3 years
de Punder (simplified)[64]			

continued

TABLE 5 Definition of the outcomes in the included model development studies (*continued*)

Name of clinical prediction model	Outcome category	Outcome definition and measurement	Predicted time point
de Vries-Bouwstra[65]	Radiographic progression (SHS)	Radiographic progression during the first year, measured as the difference between the SHS score at baseline and 1 year (SHS of > 0). Patients classed as: 1. patients with severe disease – patients with progression of radiological damage (progression score of > 0) 2. patients with mild disease – patients without progression of radiological damage (progression score of 0)	1 year
Degboé[66]	Radiographic progression (modified SHS)[a]	Radiographs scored using modified Sharp/van der Heijde method. RRP defined as an increase in a total modified SHS of ≥ 5 per year	1 year
Dirven[67]	HAQ score	Short-term functional disability (i.e. a HAQ score of ≥ 1) after 3 months of treatment	3 months
Dixey[68]	Radiographic assessment of joint damage (Larsen)	Radiographs of hands and feet taken at baseline and annually, and scored using the Larsen method. Radiographs digitised and scored randomly by one observer using the Larsen method. Larsen's erosion score used as outcome	3 years
Drossaers-Bakker[56]	Outcomes categorised as: 1. body functions and structure (impairment) 2. activities at the individual level (disability) 3. participation in society (handicap) 4. disease course	Radiographs of hands and feet scored using modified Sharp/van der Heijde method. Radiographs of large joints scored using the Larsen large joint score (0–60). Disease activity measured using the DAS (pooled ESR, SJC and Ritchie Articular Index). Cumulative disease activity measured using the AUC of all DAS assessments during 12 years' follow-up. A panel of five experienced rheumatologists jointly defined the criteria and classed patients as having a mild or severe RA course. Measured tertiles of radiographic damage (modified Sharp/van der Heijde method), disability (measured using the HAQ) and severe disease course defined as patients with either 33% highest cumulative disease activity (AUC of all observed disease activity scores) or highest tertile of radiographic damage. Identified patients in lowest (mild) and highest (severe) tertiles of each outcome measure	12 years
ESPOIR[69]	Radiographic progression (modified SHS)[a]	RRP defined as an increase of ≥ 5 on the modified SHS	1 year

Name of clinical prediction model	Outcome category	Outcome definition and measurement	Predicted time point
Forslind[70]	Joint damage and radiological progression (Larsen score)	Posteroanterior radiographs taken of hands, wrists and forefeet at baseline and after 2 years. Radiographs read by one reader. Joint damage defined as present if the end point Larsen score was ≥ 10 (median). Radiological progression was defined as present if the difference between the end point and baseline Larsen score was ≥ 8 (median)	2 years
Graell[71]	Functional disability measured using the MHAQ (MHAQ score of > 0)	MHAQ (eight questions on activities of daily living, scored 0–3) Final score was the mean score of all eight items. Disability = MHAQ score of > 0	2 years
Houseman[72]	Radiographic progression (modified SHS)	Posteroanterior radiographs of hands/wrists and feet taken at baseline and 8.2 years. Radiographic progression measured using the van der Heijde/modified Sharp method. Based on median SHS change from baseline to 8.2 years, patients categorised into low or high progression groups. Additional analyses performed using only total SHS at 8.2 years for 'absolute' radiographic outcome and cohort categorised into non-progressors and progressors using the lower quartile value (value = 6) from the distribution of total SHS (median value = 26.5)	8.2 years
Sanmartí[75]	Radiographic progression (Larsen)	Radiographs obtained of hands and feet scored using the modified Larsen method. Radiographic progression defined as a change of > 4 Larsen units between baseline and 24 months	2 years
SONORA[57]	Radiographic progression (original Sharp method)	Hand radiographs at baseline, year 1 and year 2 scored using the original Sharp method (range 0–280). Radiographic progression defined as a change of ≥ 3.54 in the TSS (as reported in the Granger *et al.*[82] external validation)	1 and 2 years
SWEFOT[73]	Radiographic progression (modified SHS method)[a]	Radiographs of hands and feet at baseline and 1 year scored using the modified SHS method. Radiographic progression defined as an increase in total SHS of ≥ 5 at 1 year	1 year
Syversen[76]	Radiographic progression (van der Heijde/modified Sharp score)	Anteroposterior radiographs of hands obtained. Radiographs scored using the van der Heijde/modified Sharp score. Radiographic progression defined as a change in the SHS of hands from baseline to 10 years of > 10 and dichotomised as the presence or absence of radiographic progression in the analyses	10 years
van Steenbergen[77]	Radiographic progression (SHS)	Radiographs of hands and feet obtained. Progression in SHS over 6 years (as a continuous outcome or categorised as no/little progression (ΔSHS of ≤ 6), moderate (ΔSHS of 7–30) or severe (ΔSHS of > 30) progression)	6 years

MHAQ, modified Health Assessment Questionnaire; NR, not reported; RRP, rapid radiographic progression; SHS, Sharp–van der Heijde score; TSS, total Sharp score.
a Studies applying the standard rapid radiographic progression definition of an increase in van der Heijde/modified Sharp score of ≥ 5 over 1 year.

TABLE 6 Definition of outcomes in the included external validation studies

Name of external validation	Outcome definition and measurement	Outcome time point (years)	Externally validated clinical prediction model(s)	Does the outcome definition in the external validation match the outcome definition in the model development? (Y/N)
De Cock[80]	RRP defined as TSS progression of ≥ 5 units per year[a]	1, 2	ASPIRE CRP	Y (two validations)
			ASPIRE ESR	Y (two validations)
			BeSt	Y (two validations)
			ESPOIR	Y (two validations)
			SWEFOT	Y (two validations)
			Syversen	N[b] (two validations)
De Cock[80]	TSS progression of ≥ 10 units from baseline to year 2 also defined as RRP. Radiographs scored using the modified Sharp/van der Heijde method (van der Heijde, 1999[18])	> 2	ASPIRE CRP	N[a]
			ASPIRE ESR	N[a]
			BeSt	N[a]
			ESPOIR	N[a]
			SWEFOT	N[a]
			Syversen	N[b]
de Punder[64]	See *Table 5*	3	BeSt	N[a]
			ESPOIR	N[a]
Granger[82]	Radiographs scored using van der Heijde/modified Sharp score at 1 year RRP defined as an increase in van der Heijde/modified Sharp score of ≥ 5 in the first year[a]	1	ASPIRE CRP	Y
			ASPIRE ESR	Y
			BeSt	Y
			ESPOIR	Y
			SONORA	N[c]
Hambardzumyan[83]	Radiographic progression (increase in van der Heijde/modified Sharp score of ≥ 5 over 1 year)[a]	1	MBDA	N[d]
Heimans[84]	Radiographs of hands and feet (blinded for patient identity) scored for the presence of erosions and JSN. *c*-statistic reported for the ability of the model to predict radiological progression (≥ 0.5-point increase in the SHS)	1	BeSt	N[e]
Markusse[85]	Radiographic progression (increase in van der Heijde/modified Sharp score of ≥ 0.5) Radiographic progression (increase in van der Heijde/modified Sharp score of ≥ 5)[a]	1, 2	MBDA	N[d] (four validations)

JSN, joint-space narrowing; N, no; RRP, rapid radiographic progression; SHS, Sharp–van der Heijde score; TSS, total Sharp score; Y, yes.

a Studies applying the standard RRP definition of an increase in van der Heijde/modified Sharp score of ≥ 5 over 1 year.

b Radiographic progression defined as a change in the SHS of hands from baseline to 10 years of > 10 and dichotomised as the presence or absence of radiographic progression in analyses.

c Radiographic progression defined as a change of ≥ 3.52 in total Sharp score (Bombardier *et al.*[57]). Granger *et al.*[82] stated that the SONORA RRP definition was an increase in the SHS of 3.54.

d MBDA developed in Centola *et al.*[61] as a disease activity test.

e BeSt (developed to predict the RRP (increase in the SHS of ≥ 5 after 1 year) used to predict radiological progression (≥ 0.5-point increase in the SHS).

As summarised above, the majority of studies considered binary outcomes, based on dichotomising an observed continuous variable. Although these outcomes are considered to be standard practice, it is worth noting that dichotomising continuous variables has previously described disadvantages.[92,93] The magnitude of the association will depend on the cut-off point used to dichotomise the variable.

As described in *Table 6*, all five external validation studies and the study by de Punder *et al.*,[64] which considered development and external validation, considered radiographic progression at 1 and/or 2 years as the outcome variable.

The external validation studies considered a total of eight previously developed clinical risk prediction models, and conducted a total of 31 external validations. In addition to describing the outcome considered in the external validation study, *Table 6* lists which clinical prediction models were considered and whether or not the outcome considered by the external validation study was consistent with that in the original model development paper.

For 17 of the 31 external validations that were conducted, the outcome considered by the external validation was different to that used for the model development. Five of these studies (labelled as N[d] in *Table 6*) externally validated the MBDA clinical prediction model (originally developed to predict the DAS28) for the prediction of radiographic progression outcomes. Ten external validations (labelled as N[a] and N[b] in *Table 6*) externally validated risk models using the outcomes at a different time point than that defined in the original model development paper. Two external validations (labelled as N[c] and N[e] in *Table 6*) externally validated risk models using different thresholds to define events, compared with that used in the original model development study.

The handling of outcomes in included studies was critically appraised using domain 3 of the PROBAST tool (see *Appendix 6*). The included studies were rated as being at a low or unclear risk of bias.

Model development

The methods used in the development of the included clinical prediction models are summarised in *Table 7*. Clinical prediction models were typically developed in the included studies using data from patients with complete cases only [i.e. having complete predictor and outcome data (e.g. Bansback,[58] Brennan,[60] Combe A,[62] Combe B,[63] de Punder,[64] de Vries-Bouwstra,[65] Degboé,[66] Dirven,[67] Dixey,[68] Drossaers-Bakker,[56] Forslind,[70] Graell,[71] Sanmartí,[75] SWEFOT[73] and Syversen[76])].

Continuous variables were frequently converted to dichotomous/trichotomous variables during the clinical prediction model development process. This was the case for seven of the externally validated models developed for the prediction of radiographic progression (all externally validated models, with the exception of MBDA). This conversion is not considered to be good practice.[31] The categorisations used for the variables included in the final models are described in *Table 8*.

Clinical prediction models were developed using multivariable regression, with the majority of studies using logistic regression [i.e. ASPIRE[78], Bansback *et al.*,[58] Berglin *et al.*,[59] BeSt,[79] Brennan *et al.*,[60] Combe *et al.* (A),[62] de Punder *et al.*,[64] Degboé *et al.*,[66] Dixey *et al.*,[68] Dirven *et al.*,[67] Drossaers-Bakker *et al.*,[56] ESPOIR,[69] Forslind *et al.*,[70] Graell *et al.*,[71] Houseman *et al.*,[72] Sanmartí *et al.*,[75] SWEFOT *et al.*[73] and Syversen[76]], as the outcome variables were binary. Backwards selection was reported for three models (i.e. Berglin *et al.*,[59] de Punder *et al.*[64] and Dirven *et al.*[67]) as being used in the selection of the final variables in the model, whereas forwards selection was used in four model development studies (i.e. Drossaers-Bakker *et al.*,[56] Forslind *et al.*,[70] Graell *et al.*[71] and Houseman *et al.*[72]). There were variations in how the selection was implemented (e.g. levels of statistical significance and combination with other techniques, such as bootstrapping, see *Table 7*).

TABLE 7 Development of the individual clinical prediction models

Name of clinical prediction model	Method of		
	Model development	Internal validation	Presentation of model
ASPIRE[78] Two models: ESR and CRP	Correlations of all baseline factors with RRP were explored. Selected factors (selection unclear) included in multivariable logistic regression	None	Risk matrices with predicted probabilities stratified by treatment
Bansback[58]	Logistic regression (multivariable, removal of predictors from full model, including covariables with a p-value of < 0.2)	Bootstrapping resampling to estimate slope shrinkage	Full model regression coefficients, nomogram
Berglin[59] Two models	Candidate predictors selected using univariable regression or clinical assumptions (description unclear). Logistic multivariable regression (backward stepwise)	Apparent performance in development cohort	OR only
BeSt[79] Two models: ESR and CRP	Logistic regression. Univariable and multivariable with backwards selection using a p-value of > 0.1. Interactions with treatment explored	Apparent performance in development cohort	OR presented for ESR and CRP models. Risk matrices with predicted probabilities presented for CRP model only, stratified by treatment
Brennan[60]	Logistic regression (multivariable, stepwise removal of predictors with a p-value of > 0.05, model checked by sequential addition of removed variables and sequential removal of remaining variables)	Randomly selected sample (prediction sample 60%, $n = 105$; validation sample 40%, $n = 70$)	Tabulation of PR for each risk category
Centola[61]	Stage 1: candidate predictors prioritised based on univariable and multivariable regression Stage 2: multivariable modelling with forward stepwise selection using three methods (OLS, LASSO, elastic net modelling) Stage 3: multivariable modelling using OLS, LASSO, elastic net method. Curds and whey multivariable response method with OLS or LASSO	Performance compared in 70/30 cross-validation (repeat training in randomly selected 70% of data and testing in remaining 30%)	Full model regression coefficients
Combe (A)[62]	Univariable analysis of all baseline variables. Logistic regression (stepwise, multivariable, selection from univariable analysis a p-value of ≤ 0.15). Results confirmed with stepwise multilinear model (with continuous random variables instead of dichotomous variables)	Apparent performance in development cohort	Full model regression coefficients

Name of clinical prediction model	Method of		Presentation of model
	Model development	Internal validation	
Combe (B)[63]	Prediction of HAQ score (continuous outcome) considered separately at 3 and 5 years. Univariable analysis of all baseline variables. Multivariable linear regression model with continuous and categorical candidate predictors	Apparent performance in development cohort	Coefficients only
de Punder[64] Simplified and extended models	Logistic regression (univariable multivariable, backwards selection with a p-value of < 0.20, as well as consideration of previously identified factors)	Bootstrapping using 300 samples for each of the five imputed data sets	Full model regression coefficients
de Vries-Bouwstra[65,a]	Model considers prediction of ΔSHS (continuous outcome). Developed using linear regression (univariable and multivariable) with categorical and continuous outcomes. Resulting predicted progression score and SD then used to calculate the probability of severe disease (ΔSHS of > 0, binary outcome) for which PPV is reported	Apparent performance in development cohort	OR only
Degboé[66] Four models	Logistic regression (univariable and multivariable)	Apparent performance in development cohort	OR only
Dirven[67]	Logistic regression. Potential confounders and candidate predictors with a p-value of < 0.1 considered in multivariable model. Backward selection process with a p-value of 0.10. Final regression model then fitted with variables categorised based on tertiles to allow matrix construction	Apparent performance in development cohort	Three matrices according to treatment group: 1. initial monotherapy 2. initial combination therapy with prednisone 3. initial combination therapy with IFX
Dixey[68] Three models	Logistic regression (univariable and multivariable)	Randomly selected sample (prediction sample 60%; validation sample 40%)	OR only
Drossaers-Bakker[56] Five outcomes with two models for each	Logistic regression (multivariable stepwise forward method)	Apparent performance in development cohort	OR only. Basic decision tree for one model
ESPOIR[69]	Logistic regression (univariable, variables with a p-value of ≥ 0.1 included in multivariable forwards and backwards selection procedure with a p-value of < 0.05)	Apparent performance in development cohort	Full model regression coefficients and prediction matrix

continued

TABLE 7 Development of the individual clinical prediction models (*continued*)

Name of clinical prediction model	Method of		Presentation of model
	Model development	Internal validation	
Forslind[70]	Logistic regression (univariable analysis used to select candidate predictors a p-value of < 0.05, then forward stepwise selection for final model)	Apparent performance in development cohort	Full model regression coefficients
Graell[71]	Univariable analysis, multivariable logistic regression (forward, stepwise). Clinically relevant interactions were considered	Apparent performance in development cohort	Full model regression coefficients
Houseman[72]	Logistic regression [univariable and multivariable, forward stepwise (entry probability = 0.05, removal probability = 0.1)]	Apparent performance in development cohort	Selected multivariable OR provided in text. Full clinical prediction model regression coefficients not provided
Sanmartí[75]	Univariable analysis used to identify significant ($p < 0.25$) variables for inclusion in multivariable logistic regression (stepwise)	Apparent performance in development cohort	Full model regression coefficients
SONORA[57]	Univariable models to identify factors, general estimation equation model used for the multivariable model	NR	OR only
SWEFOT[73] Four matrices	Logistic regression (univariable and multivariable. Parameters showing 'strongest association' chosen to make three parameter risk matrices)	None	Risk matrices show observed proportions of events rather than predicted probabilities. De Cock external validation[80] based on related conference abstract
Syversen[76] Three models	Logistic regression (variables with a p-value of < 0.15 in univariable analysis included in multivariable model)	Apparent performance in development cohort	Full model regression coefficients provided for model 1, OR only for models 2 and 3. Histogram
van Steenbergen[77]	Linear mixed-model analysis and linear regression analysis, with continuous and categorical outcomes considered for model development	Apparent performance in development cohort	Presents performance measures only

LASSO, least absolute shrinkage and selection operator; NR, not reported; OLS, ordinary least squares; PR, predicted risk; RRP, rapid radiographic progression; SHS, Sharp score.

TABLE 8 Predictors included in individual final models[a]

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
ASPIRE[78] CRP/ESR models	SJC28 (< 10, 10–17 or > 17)	CRP level (< 0.6 mg/dl, 0.6–3 mg/dl, > 3 mg/dl) or ESR (< 21 mm/hour, 21–50 mm/hour or > 50 mm/hour) RF (< 80 U/ml, 80–200 U/ml or > 200 U/ml)	–	–		MTX monotherapy or MTX and IFX
Berglin[59] Two models	Model 1: SJC28 Models 1 and 2: therapeutic response (yes/no) (EULAR response criteria no vs. good/ moderate response)	Model 1: anti-CCP (yes/no) Model 2: ESR Model 2: IgA RF (yes/no)	–	–	–	–
BeSt[79]	–	ACPA and/or RF 0, 1 or 2 positive, a CRP level of < 10 mg/l, 10–35 mg/l or ≥ 35 mg/l	Erosion score of 0, 1–4 or ≥ 4	–	–	Treatment strategy (initial monotherapy, initial combination with prednisone, initial combination with IFX)
Brennan[60]	Involvement of ≥ 2 large joints Disease duration of > 90 days (i.e. 12.9 weeks) at first presentation	RF positive (titre of ≥ 1 : 80)	–	–	–	–

continued

TABLE 8 Predictors included in individual final models[a] (*continued*)

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
Combe (A)[62]	Model 2 (high > 4 Sharp score): pain at ≥ 59 mm (median value at baseline on a VAS scale of 0–100)	Model 1 (radiographic progression): an ESR of ≥ 33 mm/hour (median value at baseline) Models 1 (radiographic progression) and 2 (high > 4 Sharp score): IgM RF positivity (≥ 20 IU/ml) (categorical low/absent or high/present)	Model 1 (radiographic progression): erosions score of ≥ 1 (categorical low/absent or high/present) Model 2 (high > 4 Sharp score): initial Sharp score (categorical low/absent or high/present)	–	Models 1 (radiographic progression) and 2 (high > 4 SHS): HLA-DRB1*04 positivity	–
de Punder[64] Simplified and extended models	–	Extended: anti-CCP and/or RF (0, 1 or 2 positive), an ESR of < 25 mm/hour, 25–50 mm/hour or > 50 mm/hour Simplified: dichotomised anti-CCP level of > 25 U/ml (> 10 U/l in frozen samples) and a dichotomised ESR of > 25 mm/hour	Extended: erosions (0 Ratingen points, 1–5 Ratingen points, 6–10 Ratingen points or > 10 Ratingen points) Simplified: dichotomised baseline Ratingen score of ≥ 1 point	Aged < 45 years, 45–64 years, > 64 years at diagnosis and female sex	–	–
de Vries-Bouwstra[65,b]	Bilateral compression pain in metatarsophalangeal joints (categorical), duration of symptoms at presentation (> or ≤ 6 weeks), HAQ score (continuous), morning stiffness duration (continuous), Ritchie Articular Index score (continuous), total SJC (max 22) (continuous), VAS disease activity (continuous)	ESR (continuous), IgM RF positivity [≥ 5 U (categorical)]	Presence of erosions on radiographs (categorical), SHS (continuous)	Age (continuous) and sex	SE hetero- or homozygosity (categorical)	–

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
Degboé[66,c] Four models	–	Model 1: anti-CCP-2 positivity and a CRP level of > 10 mg/l Model 2: anti-MCV positivity, a CRP level of > 10 mg/l and RF positivity Model 3: AhFibA positivity, a CRP level of > 10 mg/l Model 4: high anti-CCP2 or AhFibA titres, high anti-MCV titres and a CRP level of > 10 mg/l Model 2: RF positivity	Models 1 and 4: erosions at baseline	Model 3: age at RA onset	–	–
Dixey[68] Three models	All continuous variables categorised into quartiles Model 2: SJC Model 2: nodules	Models 1 and 3: ESR Model 1: RF positivity	Model 2: joint score Models 2 and 3: Larsen score	–	–	–
Drossaers-Bakker[56]	Mild radiographic damage (all): SJC Mild radiographic damage (selected): SJC Severe radiographic damage (all): SJC Severe radiographic damage (selected): SJC	Mild radiographic damage (all): RF positivity Mild radiographic damage (selected): RF positivity Severe radiographic damage (all): RF positivity Severe radiographic damage (selected): RF positivity	Mild radiographic damage (all): erosive at study start Mild radiographic damage (selected): erosive at study start Severe radiographic damage (all): erosive at study start Severe radiographic damage (selected): erosive at study start	–	Mild radiographic damage (all): SE Mild radiographic damage (selected): – Severe radiographic damage (all): RAP Severe radiographic damage (selected): –	–

continued

TABLE 8 Predictors included in individual final models[a] (*continued*)

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
ESPOIR[69]	SJC28 (< 14, 14–20 or ≥ 20)	ACPA positive/negative CRP ≥ 35 mg/l, 4 mg/l ≤ CRP < 35 mg/l, CRP < 4 mg/l	Presence/absence of typical RA erosions on radiographs	–	–	–
Forslind[70] Two models	–	(Continuous variables categorised by median baseline value as cut-off point; anti-CCP and RF positivity) Model 1 (radiological damage) and model 2 (radiological progression): anti-CCP positivity Models 1 (radiological damage) and 2 (radiological progression): ESR	Models 1 (radiological damage) and 2 (radiological progression): Larsen score	–	–	–
Houseman[72] Two models	–	Radiographic progression model: anti-CCP positivity (titre of > 6 U/ml) (taken at the 8.2-year follow-up visit) and baseline MMP-3 elevation (> 85.79 ng/ml) Absolute radiographic outcome model: anti-CCP positivity (titre of > 6 U/ml) (taken at the 8.2-year follow-up visit) and baseline MMP-3 level (> 85.79 ng/ml)	Radiographic progression model: baseline SHS (SHS of > 7)	–	–	–

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
Sanmartí[75]	–	Anti-CCP positive	–	Sex	HLA-DRB1*04 positive	–
SONORA[57]	DAS28 (≤ 3.2 or > 3.2)	Anti-CCP (≤ 20 UI/l or > 20 UI/l)	SHS (0, 1–5 or 6–10)	–	–	–
SWEFOT[73] Original, sex and treatment models	–	Original, sex and treatment models: CRP level (< 10 mg/dl, 10–35 mg/dl or > 35 mg/dl)	Original, sex and treatment models: presence of erosions	Original, sex and treatment models: current smoking Sex model	–	Treatment model (treatment month 3–12): whole group, MTX monotherapy, combination with IFX, combination with SSZ and HCQ
Syversen[76]	–	Anti-CCP positivity (> 25 U/ml), ESR (> 20 mm/hour) and IgM RF positivity (> 25 U/ml)	–	Sex	–	–
van Steenbergen[77]	Traditional factors, including localisation of initial joint symptoms, SJC66	Traditional factors, including presence of ACPA, presence of ESR and presence of RF	–	Traditional factors, including age, sex and symptom duration at first visit	Single nucleotide polymorphisms/genetic variants as listed in table footnotes[d]	Treatment effects (initial treatment with NSAIDs; initial treatment with HCZ or SSZ; initial treatment with MTX)
Models predicting HAQ score or disease course						
Bansback[58]	DAS28 year 1 HAQ score at baseline and year 1 Functional grade at baseline (I, II, III and IV) and year 1 (I, II, III and IV)	Haemoglobin level at baseline	Larsen score at baseline	Carstairs deprivation index (1, 2, 3, 4 or 5)	–	–

continued

TABLE 8 Predictors included in individual final models[a] (*continued*)

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
Combe (B)[63] Model 1: 5-year HAQ score Model 2: 3-year HAQ score	Model 1 and 2: HAQ score Model 1: Ritchie Articular Index	Model 1: CRP Model 1: ESR	–	–	–	–
Dirven[67]	HAQ score of < 1.38, 1.38–2.00 or > 2.00 Ritchie Articular Index score of < 10, 10–16 or > 16 VAS pain score of < 40, 40–60 or > 60	–	–	–	–	Monotherapy, combination therapy with prednisone, combination therapy with IFX
Drossaers-Bakker[56]	Mild HAQ (all): HAQ score Mild HAQ (selected): HAQ score Severe HAQ (all): HAQ score Severe HAQ (selected): HAQ score Severe disease course (all): SJC and HAQ score Severe disease course (selected): SJC and Ritchie score	–	Mild HAQ (all): erosive at study start Mild HAQ (selected): erosive at study start Severe HAQ (all): – Severe HAQ (selected): – Severe disease course (all): – Severe disease course (selected): –	–	Mild HAQ (all): – Mild HAQ (selected): – Severe HAQ (all): – Severe HAQ (selected): – Severe disease course (all): SE Severe disease course (selected): –	–
Graell[71]	Baseline MHAQ score (> 0.5)	RF positivity	–	Age	–	–

Name of clinical prediction model	Clinical prediction model variables					
	Clinical	Biomarkers	Radiography	Demographic	Genetic	Treatment
Models developed as a measure of disease activity						
Centola[61]	–	12 biomarker model: 1. TNF receptor I 2. interleukin 6 3. vascular cell adhesion molecule I 4. epidermal growth factor 5. VEGF-A 6. cartilage glycoprotein 39 7. MMP-1 8. MMP-3 9. serum amyloid A 10. leptin 11. resistin 12. CRP	–	–	–	–

A, adenine; AhFibA, anti-human citrullinated fibrinogen anti-body; C, cytosine; CD40, cluster of differentiation 40; DKK-1, dickkopf WNT signalling pathway inhibitor 1; G, guanine; GrzB, granzyme B; HCZ, hydrochlorothiazide; IgA, immunoglobulin A; IgM, immunoglobulin M; IL-15, interleukin 15; IL2RA, interleukin 2 receptor alpha chain; IL4R, interleukin 4 receptor; HLA, human leucocyte antigen; MMP, matrix metalloproteinase; NR, not reported; OPG, osteoprotegerin; RAP, rheumatoid arthritis protected; rs, reference SNP cluster ID; SE, shared epitope; SPAG16, sperm-associated antigen 16; T, thymine; VAS, visual analogue scale; VEGF, vascular endothelial growth factor.

a Details of the handling of continuous and categorical variables are reported when available.

b All available and potentially prognostic baseline variables used without any selection of variables.

c Anti-CCP, positive ≥ 40 U/ml; antimutated citrullinated vimentin, positive > 35 UA/ml; and AhFibA, positive > 0.119 AU.

d Generic variants located in/near gene(s) *HLA-DRB1*, *CD40*, *IL-15*, *DKK-1*, *IL2RA*, *GRZB*, *IL-4R*, *SPAG16*, *C5orf30*, *MMP-9*, *rs1465788*, *OPG*.

The BeSt model development (by Visser *et al.*[79]) and the model by Graell *et al.*[71] were the only two model development studies to specifically describe having considered the presence of interactions between variables. As Visser *et al.*[79] also considered the effect of treatment, this is of relevance to review 2 and is discussed in further detail in *Results: synthesis of primary studies*.

The majority of the included clinical prediction model development studies used a limited form of internal validation, with apparent predictive performance tested within the original development data set (TRIPOD statement type 1a). Testing the apparent performance of a clinical prediction model using the same data in which the model was developed can lead to optimistic estimates of performance.[26] This is attributed to 'overfitting', whereby there are too few outcome events in relation to the number of candidate predictors. Therefore, the performance estimates derived from the included TRIPOD statement type 1a studies should be viewed with caution in the absence of more robust validation.

Ideally, clinical prediction model development studies should include a method of internal validation to quantify any optimism in the predictive performance. Two studies (i.e. Bansback *et al.*[58] and de Punder *et al.*[64]) used bootstrapping for estimating model performance (i.e. TRIPOD statement type 1b). A further two studies (i.e. Brennan *et al.*[60] and Dixey *et al.*[68]) used a data-splitting approach.

One study tested the performance of its developed clinical prediction models on separate data from a different study (TRIPOD statement type 3). Vastesaeger *et al.*[78] tested the performance of their ASPIRE model for the prediction of radiographic progression in data from ATTRACT (Anti-TNF trial in rheumatoid arthritis with concomitant therapy). As stated previously, as the ATTRACT trial was conducted in patients with established RA, this validation is outside the scope of this assessment and so is not considered further.

The form in which the clinical prediction models were presented determines the ease with which they may be used in clinical practice, and not all of the model development studies presented their models in sufficient detail for them to be applied to other populations. In order for clinicians to directly apply a model, one option is to present the full model regression coefficients (including the intercept term), which allows the model to be used to generate absolute risks. Alternatively, the absolute risks for each individual combination of variables (e.g. in a risk matrix format) could be presented. Of the 39 clinical prediction models, 18 were presented in a useable format.

Of the eight externally validated risk models, the majority were presented as risk matrices in the published report: ASPIRE[78] (ESR and CRP), BeSt,[79] Dirven *et al.*[67] and ESPOIR.[69] Two externally validated clinical prediction models (MBDA[61] and Syversen *et al.*[76]) presented the full model regression coefficients. Syversen *et al.*[76] also presented the final model graphically using a histogram. The SWEFOT[73] models were not presented in a useable format in the model development publication, and for this reason they were not tested in the Granger *et al.*[82] external validation. However, the main SWEFOT model was considered in the De Cock *et al.*[80] external validation, based on results that are available in conference proceedings.[73]

Some studies were noted as reporting 'OR only' in *Table 7*, indicating that the coefficient of the intercept term in the regression was not provided and, therefore, the model would not be able to be used to provide absolute risks.

The final predictors selected for use in the included clinical prediction models are presented in *Table 8*. The prognostic variables selected for consideration in the assessment in conjunction with clinical advisors were very commonly incorporated as predictors in the final clinical prediction models. However, the continuous variables were generally categorised, with the models applying a range of differing thresholds in their construction.

Additional clinical predictors

The clinical prediction models also included the following additional clinical predictors:

- bilateral compression pain (i.e. de Vries-Bouwstra *et al.*[65])
- functional grade (i.e. Bansback *et al.*[58])
- localisation of initial joint symptoms (i.e. van Steenbergen *et al.*[77])
- morning stiffness (i.e. de Vries-Bouwstra *et al.*[65])
- nodules [i.e. Dixey *et al.* (2)[68]]
- Ritchie Articular Index [i.e. de Vries-Bouwstra *et al.*,[65] Combe *et al.* (B1),[63] Dirven *et al.*,[67] Drossaers-Bakker *et al.*[56] (severe disease course, selected)]
- therapeutic response [EULAR response criteria: no vs. good/moderate response; i.e. Berglin *et al.* (1),[59] Berglin *et al.* (2)[59]]
- visual analogue scale disease activity (i.e. de Vries-Bouwstra *et al.*[65])
- visual analogue scale pain [i.e. Dirven *et al.*,[67] Combe *et al.* (A2)[62]].

Additional biomarkers

The following biomarkers were also included in the two final clinical prediction models:

- haemoglobin level (i.e. Bansback *et al.*[58])
- matrix metalloproteinase (MMP)-3 [i.e. Houseman *et al.* (radiographic progression model)[72]]
- additional biomarkers included in MBDA [i.e. Centola *et al.*[61] (see *Table 8*)].

Additional demographic predictors

Demographic variables were included in the following final clinical prediction models:

- age [i.e. de Punder *et al.* (extended),[64] de Vries-Bouwstra *et al.*,[65] Degboé *et al.* (3),[66] Graell *et al.*[71] and van Steenbergen *et al.*[77]]
- Carstairs Deprivation Index (i.e. Bansback *et al.*[58])
- sex [i.e. de Vries-Bouwstra *et al.*,[65] Sanmartí *et al.*,[75] SWEFOT *et al.* (sex),[73] Syversen *et al.*,[76] van Steenbergen *et al.*[77]].

Genetic predictors

A minority of clinical prediction models also integrated genetic predictors:

- RA protected [i.e. Drossaers-Bakker *et al.* (severe radiographic damage, all)[56]]
- shared epitope (SE) [i.e. de Vries-Bouwstra *et al.*,[65] Drossaers-Bakker *et al.* (mild radiographic damage, all),[56] Drossaers-Bakker *et al.* (severe disease course, all)[56]]
- HLA-DRB1*04 positivity [i.e. Combe *et al.* (A1),[62] Combe *et al.* (A2),[62] Sanmartí *et al.*[75]]
- single nucleotide polymorphisms located in/near human leucocyte antigen (*HLA*)-*DRB1* (SE), *CD40* (cluster of differentiation 40), *IL-15* (interleukin 15), *DKK-1* (dickkopf WNT signalling pathway inhibitor 1), *IL2RA* (interleukin 2 receptor alpha chain), *GRZB* (granzyme B), *IL4R* (interleukin 4 receptor), *SPAG16* (sperm-associated antigen 16), *C5orf30* (chromosome 5 open reading frame 30), *MMP-9*, *rs* (reference single nucleotide polymorphisms cluster ID) *1465788* and *OPG* (osteoprotegerin) (i.e. van Steenbergen *et al.*[77]).

Treatment

The ASPIRE CRP,[78] ASPIRE ESR,[78] BeSt,[79] Dirven[67] and SWEFOT (treatment)[73] clinical prediction models were developed using RCT data and included treatment as a variable in the final model. For all of these studies, the final clinical prediction model was presented using separate risk matrices according to treatment group. Although separate matrices by treatment were presented, the final models did not include treatment by predictor interaction terms (as is considered in review 2). This assumes that all predictors are prognostic for all treatments, and that the magnitude of the prognostic effect of each predictor does not vary by treatment, which is unlikely to be true in practice. As noted in *Model development*, Visser *et al.*[79] assessed the interaction between predictors, but found these to be not statistically significant and, therefore, did not include

interactions in the final model. It should be noted that the absence of evidence for interaction effects is not evidence of the absence of interaction effects, and such terms should be retained in a model if there is reason to believe them to be real effects, irrespective of their statistical significance.

It was considered in PROBAST domain 2 whether or not all (final) predictors would be available at the time at which the model was intended to be used. The majority of predictors were considered to be widely available. Data for the Carstairs Deprivation Index, SE, HLA-DRB1*04 testing, RA protected, MMP-3 and genetic tests may be less accessible.

The majority of the model development studies were rated as having an unclear risk of bias for domain 2. All external validation studies were classed as being at a low risk of bias.

Performance results: clinical prediction model development studies

The performance of the included clinical prediction models, as reported in the original model development studies, is presented in *Table 9*. Discrimination (using the *c*-statistic) was recorded when available, in addition to information relating to the model calibration and overall model goodness of fit. Additional performance measures presented by the studies are shown in *Appendix 7*. Unless otherwise indicated, sample sizes and the number of events refer to the sample used for the final multivariable prediction models.

As previously discussed, good discriminative ability in the population used to develop the model would be expected. The external validation of all models in the same data set or multiple data sets is required to objectively compare the reported *c*-statistics. The results of these external validations are presented in *Results: external validation studies*.

Models predicting radiographic joint damage

Discrimination was reported using the *c*-statistic by six of the studies,[64,66,69,72,77,79] which considered a total of 13 clinical prediction models. *c*-statistics for models predicting radiographic joint damage are summarised in a forest plot in *Figure 6*.

The BeSt model[79] for the prediction of radiographic progression at 1 year demonstrated reasonably good discrimination, which was broadly comparable between the CRP and ESR models (CRP model *c*-statistic 0.81, 95% CI 0.77 to 0.86; ESR model *c*-statistic 0.80, 95% CI 0.75 to 0.85).

The de Punder extended and simplified models[64] predicted radiographic progression at 3 years. The *c*-statistics obtained indicated moderate predictive performance (extended *c*-statistic 0.77, 95% CI 0.72 to 0.81; simplified *c*-statistic 0.75, 95% CI 0.70 to 0.80).

Four clinical prediction models were produced by Degboé[66] for the prediction of radiographic progression at 1 year. The apparent performance (TRIPOD statement type 1a) of these models was reported. The *c*-statistics were lower than for other models predicting radiographic progression over 1 year [anti-CCP *c*-statistic 0.65, 95% CI 0.60 to 0.70; antimutated citrullinated vimentin (anti-MCV) *c*-statistic 0.63, 95% CI 0.58 to 0.68; anti-human citrullinated fibrinogen anti-body (AhFibA) *c*-statistic 0.65, 95% CI 0.60 to 0.71; high-level ACPA titre *c*-statistic 0.65, 95% CI 0.60 to 0.70].

The ESPOIR clinical prediction model[69] for radiographic progression at 1 year yielded a *c*-statistic of 0.754 [95% CI not reported (TRIPOD statement type 1a)].

Two clinical prediction models were constructed by Houseman *et al.*[72] The apparent performances (TRIPOD statement type 1a) were reported. The first model (for radiographic progression at 8.2 years) showed good performance (with a *c*-statistic of 0.87). The second model (for absolute radiographic outcome at 8.2 years) showed similarly good discriminatory abilities (with a *c*-statistic of 0.84). It was noted that anti-CCP

TABLE 9 Performance results from clinical prediction model development studies

Name of clinical prediction model(s)	Outcome definition	Sample size (*n*)	Total number of observed events	Overall model fit	Discrimination, *c*-statistic (95% CI)	Calibration/assessment of overfitting
Prediction of radiographic joint damage (ΔSHS ≥ 5 at 1 year)						
ASPIRE[78] CRP ESR	ΔSHS of ≥ 5 at 1 year	Total trial population, $n = 1049$	≦ 124 (MTX monotherapy, 22.8%; IFX and MTX, 8.3%)	NR	NR	NR
BeSt[79] CRP ESR	ΔSHS of ≥ 5 at 1 year	465	102	CRP: Nagelkerke's $R^2 = 0.31$ ESR: Nagelkerke's $R^2 = 0.29$	CRP: 0.81 (0.77 to 0.86) ESR: 0.80 (0.75 to 0.85)	NR
Degboé[66] Anti-CCP Anti-MCV AhFibA High ACPA titre	ΔSHS of ≥ 5 at 1 year	566	145	NR	Anti-CCP: 0.65 (0.60 to 0.70) Anti-MCV: 0.63 (0.58 to 0.68) AhFibA: 0.65 (0.60 to 0.71) High ACPA titre: 0.65 (0.60 to 0.70)	NR
ESPOIR[69]	ΔSHS of ≥ 5 at 1 year	370	41 (11.1%)	NR	0.75	Hosmer–Lemeshow described but not presented
SWEFOT[73] Four models	ΔSHS ≥ 5 at 1 year	269	72	NR	NR	NR

continued

TABLE 9 Performance results from clinical prediction model development studies (*continued*)

Name of clinical prediction model(s)	Outcome definition	Sample size (*n*)	Total number of observed events	Overall model fit	Discrimination, *c*-statistic (95% CI)	Calibration/assessment of overfitting
Prediction of radiographic joint damage (other outcome definitions)						
de Vries-Bouwstra[65]	ΔSHS of > 0 at 1 year	95	69	$R^2 = 0.36$	NR	Calibration plot/table presented
SONORA[57]	ΔSHS of ≥ 3.54[a] at 1 year	994	Year 1: 10.4%	NR	NR	NR
Year 1	ΔSHS of ≥ 3.54 at 2 years		Year 2: 11.7%			
Year 2						
Combe (A)[62]	Total damage: ΔSHS of ≥ 3.4	172	Total damage: 71	NR	NR	NR
Total damage	Erosions: ΔSHS of ≥ 3.2 at 3 years		Erosions: 55			
Erosions						
van Steenbergen[77]	ΔSHS at 6 years	239	72, 99, 68 (none, moderate, severe)	Treatment and traditional: $R^2 = 0.36$	Treatment and traditional $c = 0.78$ (0.73 to 0.82)	NR
Treatment and traditional	None: ΔSHS of ≤ 6					
	Moderate: ΔSHS of 7–30			Treatment and traditional and genetic $R^2 = 0.44$	Treatment and traditional and genetic $c = 0.82$ (0.77 to 0.86)	
Treatment and traditional and genetic[b]	Severe: ΔSHS of > 30					
Houseman[72]	ΔSHS of > 10.5	58	29	NR	0.87	NR
Change in the SHS	Total SHS of > 6		44	NR	0.84	
Absolute SHS	Both at 8.2 years					
Syversen[76]	ΔSHS of > 10 at 10 years	125	74	NR	NR	NR
Brennan[60]	Based on Larsen score at 1 year	175	Prediction: 37/105	NR	NR	NR
			Validation: 26/70			
			Total: 63/175			

Name of clinical prediction model(s)	Outcome definition	Sample size (*n*)	Total number of observed events	Overall model fit	Discrimination, *c*-statistic (95% CI)	Calibration/assessment of overfitting
Berglin[59] Model 1 Model 2	Based on Larsen score at 2 years	Baseline, $n = 138$	NR for total sample	Model 1: Nagelkerke's $R^2 = 0.21$ Model 2: Nagelkerke's $R^2 = 0.24$	NR	NR
Forslind[70] Joint damage Progression	Joint damage: Larsen score ≥ 10 at 2 years Progression: Δ Larsen score ≥ 10 at 2 years	333	NR	Joint damage: Nagelkerke's $R^2 \geqq 0.5$ Progression: Nagelkerke's $R^2 \geqq 0.4$	NR	NR
Sanmartí[75]	Based on Larsen score at 2 years	105	34 (32%)	NR	NR	NR
Dixey[68] Model 1 Model 2 Model 3	Larsen score at 3 years	Overall (60% development sample): Model 1 – 587 (365) Model 2 – 850 (518) Model 3 – 649 (370)	Number in development population: Model 1 – 210 erosive Model 2 – 121 severe Model 3 – 62 severe	NR	NR	NR
de Punder[64] Extended Simplified	≥ 5 Ratingen points at 3 years	425	175	NR	Extended: 0.77 (0.72 to 0.81) Simplified: 0.75 (0.70 to 0.80)	Extended: Hosmer–Lemeshow, $p = 0.41$–0.85. Shrinkage factor: 0.90 (95% CI 0.88 to 0.92). Calibration slope = 1.0 (95% CI 0.82 to 1.21) Simplified model: Hosmer–Lemeshow, $p = 0.87$–0.99. Shrinkage factor: 0.98 (95% CI 0.96 to 1.0). Calibration slope = 1.1 (95% CI 0.89 to 1.33)

continued

TABLE 9 Performance results from clinical prediction model development studies (*continued*)

Name of clinical prediction model(s)	Outcome definition	Sample size (*n*)	Total number of observed events	Overall model fit	Discrimination, *c*-statistic (95% CI)	Calibration/assessment of overfitting
Prediction of HAQ score						
Dirven[67]	≥ 1 at 3 months	497	199 (40%)	Nagelkerke's $R^2 = 0.29$	0.78 (0.74 to 0.82)	NR
Bansback[58]	≥ 1.5 at 5 years	985[c]	298	Nagelkerke's $R^2 = 0.39$	0.82	Slope shrinkage of 0.89 based on 200 bootstrap samples
Combe (B)[63]	Continuous variable at 5 years (3-year data not shown)	156	N/A (continuous variable)	NR	NR	NR
Prediction of MHAQ score						
Graell[71]	MHAQ score of > 0 at 2 years	105	28	NR	NR	NR
Prediction radiographic damage, HAQ score and severe disease course at 12 years						
Drossaers-Bakker[56,d]	Mild/severe SHS at 12 years HAQ score and severe disease course at 12 years	Total population, $n = 112$	Unclear	NR	NR	NR
Prediction of DAS28						
MBDA (Centola *et al.*)[61]	DAS28-CRP ≥ 2.67 at 3 months	708 (stage 3 algorithm training)	NR	NR	NR for final MBDA model	NR

anti-MCV, antimutated citrullinated vimentin; N/A, not applicable; NR, not reported.

a Outcome definition as reported by Granger *et al.*[82] external validation study.

b Traditional risk factors studied were age, sex, symptom duration at first visit, localisation of initial joint symptoms (SJC66), presence of ACPA, presence of RF and ESR. The initial treatment strategy differed for different inclusion periods [initial NSAIDs (non-steriodal anti-inflammatory drugs), initial HCQ/SSZ and initial MTX]. As the severity of progression differed for these three groups, treatment effects were incorporated into the analyses.

c Total population size. Number contributing to the multivariable model is lower but unclear.

d Although the publication by Drossaers-Bakker *et al.*[56] reported multiple prediction models, the reporting of these was considered to be unclear and is therefore included above as one entry.

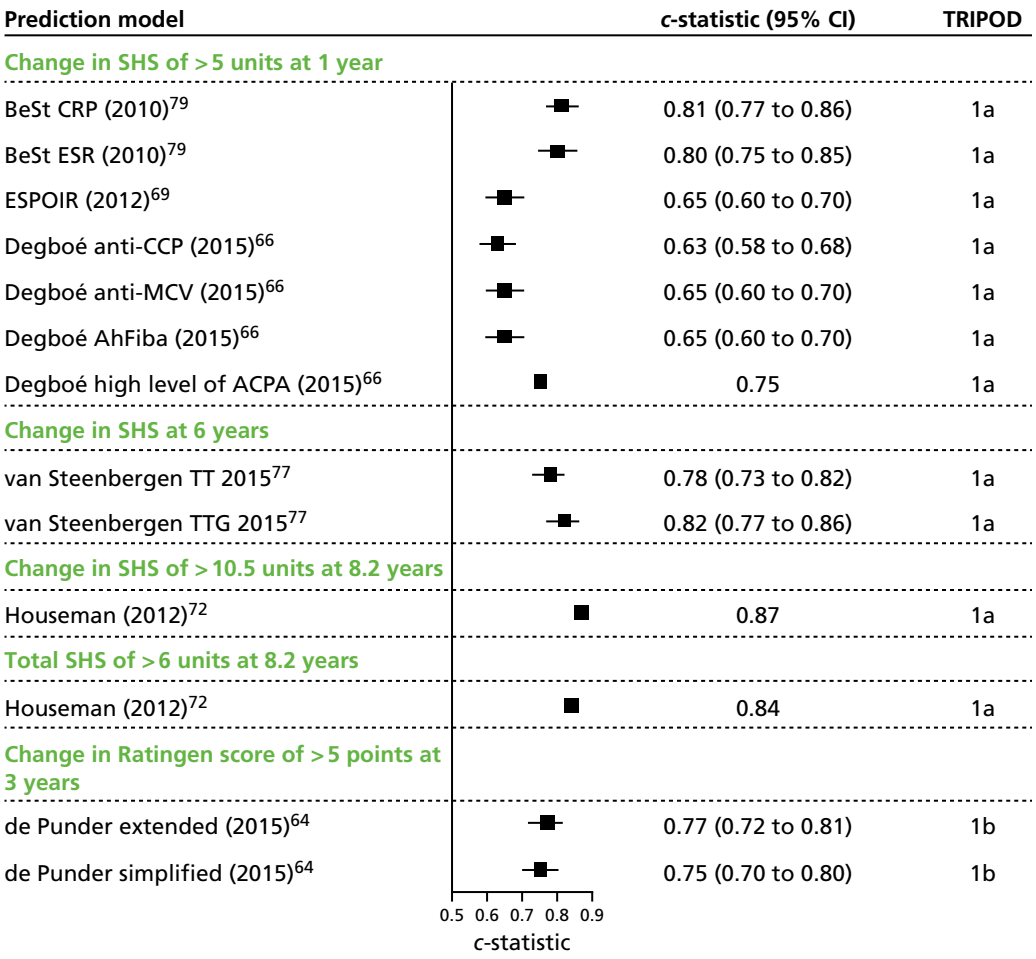

FIGURE 6 Forest plot of predictive performance of the included clinical prediction models for radiographic joint damage based on internal validation. Anti-MCV, antimutated citrullinated vimentin; TT, treatment and traditional factors; TTG, treatment, traditional and genetic factors.

positivity was measured at the 8.2-year follow-up point, as opposed to baseline or in the early stages of disease, as discussed in *Description of predictors*.

c-Statistics were presented for the clinical prediction models by van Steenbergen *et al.*[77] for predicting radiographic progression at 6 years. For this study, an outcome variable with three categories was considered and the reported *c*-statistics were computed using Harrell's *c*-statistic for ordinal data.[37] The model that included treatment plus traditional (i.e. selected demographic, clinical and biomarker) variables had a moderate performance (*c*-statistic 0.78, 95% CI 0.73 to 0.82). The addition of genetic factors to the model (treatment and traditional and genetic) increased the discrimination of the model slightly (*c*-statistic 0.82, 95% CI 0.77 to 0.86).

The model goodness of fit (R^2) was only rarely reported. Low Nagelkerke's R^2 values were obtained for the Berglin models (model 1: 0.21; model 2: 0.24);[59] Forslind model 1 (radiological damage)[70] yielded a Nagelkerke's R^2 value of 0.5, whereas the fit for model 2 (radiological progression) was slightly poorer at 0.4. For the de Vries-Bouwstra model,[65] the fit (R^2) was 0.36. The R^2 for the van Steenbergen models[77] increased when genetic factors were added to treatment plus traditional factors (0.43 from 0.36, an increase of 0.07; $p = 0.06$, adjusted R^2 increase = 0.03). Although Nagelkerke's R^2 was reported in several publications and used to compare the overall model fit of competing models, it does not provide an assessment of the models' predictive performance. A model may have a low R^2 value while still providing a useful prediction tool.

Model calibration was not frequently reported. De Punder *et al.*[64] assessed calibration using the Hosmer–Lemeshow test, with *p*-values being large ($p > 0.4$) for all clinical prediction models, indicating that there was no evidence to suggest a poor model fit. Calibration slopes and shrinkage factors were also presented for the de Punder extended model[64] (shrinkage factor 0.90, 95% CI 0.88 to 0.92; calibration slope 1.0, 95% CI 0.82 to 1.21) and the de Punder simplified[64] models (shrinkage factor 0.98, 95% CI 0.96 to 1.0; calibration slope 1.1, 95% CI 0.89 to 1.33). For the ESPOIR model,[69] the use of the Hosmer–Lemeshow test was described but not presented.

Models predicting Health Assessment Questionnaire score/disease course

The Bansback model[58] predicted a HAQ score of ≥ 1 at 5 years. The internal validation of the model resulted in a *c*-statistic of 0.82.

The goodness of fit of the Bansback model was 0.39 (Nagelkerke's R^2).[58] The reported Nagelkerke's R^2 value for the Dirven model was 0.29.[67]

Secondary predictive performance measures (e.g. accuracy, sensitivity, specificity, PPV, NPV) are presented when these were available (see *Tables 31* and *32*). Several studies presented performance measures based on a specific threshold to define an event, when thresholds were often defined according to the study population, and thus differed across studies. These measures are less informative than overall performance measures, such as the *c*-statistic. They are presented for completeness but are not discussed further.

Results: external validation studies

The performance results of the external validation studies are summarised in *Table 10*. Six external validation studies (including one combined model development/external validation study) were identified that tested the performance of a total of eight previously developed clinical prediction models. All studies focused on the prediction of radiographic joint damage.

The De Cock *et al.*[80] external validation study considered six previously developed clinical prediction models (i.e. ASPIRE[94] CRP, ASPIRE[94] ESR, BeSt,[79] Syversen,[76] SWEFOT[73] and ESPOIR[69]). Note that the Syversen prediction model[76] was referred to as SWEFOT 1 in the De Cock *et al.* external validation,[80] whereas the SWEFOT model by Saevarsdottir *et al.*[73] was denoted as SWEFOT 2. De Cock *et al.*[80] presented results for three different time intervals: first year (baseline to year 1); second year (year 1 to year 2); and over 2 years (baseline to year 2). For this final assessment, progression was defined as total Sharp score (TSS) of > 10 over 2 years, as opposed to a TSS of > 5 over 1 year and, as such, differs from the outcome definition used in the model development studies.

The Granger external validation study[82] presented results from four clinical prediction models that had been developed in other populations. Results were also presented for the ESPOIR model[69] and an updated mESPOIR[82] model; however, given that the ESPOIR model[69] was initially developed in this population, this should not be considered as an external validation. The results are presented here for completeness, but are not used for the subsequent meta-analysis. Granger *et al.*[82] considered two versions of each model, with the first being based on the published model and the second recalibrated with a new estimate of the model intercept, but fixing the regression coefficients to be the same. The models were recalibrated on a subsample of one-third of the ESPOIR[69] population and then tested on the remaining two-thirds of the population. Details of how the calibration sample was chosen were not provided.

The BeSt[79] and ESPOIR[69] models were also externally validated in the report of the de Punder models.[64] Heimans *et al.*[84] externally validated the BeSt model; however, the only version of the *c*-statistic that was reported was based on a different definition of the outcome (i.e. a SHS of > 0.5 rather than SHS of > 5) than that was used to derive the model and to assess performance in the other external validation studies. Hambardzumyan *et al.*[83] and Markusse *et al.*[85] externally validated MBDA.

TABLE 10 Performance results from external validation studies

Name of external validation study (submodels)	Clinical prediction model	Sample size (*n*)	Total number of observed events	Overall model fit (Nagelkerke's R^2)	Discrimination *c*-statistic (95% CI)	Calibration/assessment of overfitting
Prediction of radiographic joint damage (ΔSHS of > 5 at 1 year)						
De Cock first year[80]	ASPIRE CRP	74[a]	4	NR	0.68	O : E ratio:[b] 0.35
	ASPIRE ESR	74			0.68	0.42
	BeSt	73			0.60	0.27
	Syversen	73			0.34	0.08
	SWEFOT	74			0.52	0.20
	ESPOIR	73			0.35	0.31
De Cock second year[80]	ASPIRE CRP	74	5	NR	0.65	NR
	ASPIRE ESR				0.37	
	BeSt				0.50	
	Syversen				0.54	
	SWEFOT				0.44	
	ESPOIR				0.50	
Granger[82]	ESPOIR	370	41	0.17	0.75 (0.70 to 0.84)	Hosmer–Lemeshow test:[c] 0.96
	mESPOIR			0.30	0.82 (0.76 to 0.89)	0.55
	SONORA			0.00	0.76 (0.68 to 0.83)	< 0.01
	SONORA (recalculated)			0.00	0.76 (0.69 to 0.83)	< 0.01
	BeSt			0.00	0.73 (0.65 to 0.81)	< 0.01
	BeSt (recalibrated)			0.00	0.73 (0.64 to 0.80)	< 0.01
	ASPIRE ESR			0.00	0.54 (0.45 to 0.64)	< 0.01
	ASPIRE ESR (recalibrated)			0.00	0.54 (0.46 to 0.64)	< 0.01
	ASPIRE CRP			0.00	0.62 (0.54 to 0.69)	0.25
	ASPIRE CRP (recalibrated)			0.00	0.62 (0.41 to 0.60)[d]	< 0.01

continued

TABLE 10 Performance results from external validation studies (*continued*)

Name of external validation study (submodels)	Clinical prediction model	Sample size (*n*)	Total number of observed events	Overall model fit (Nagelkerke's R^2)	Discrimination *c*-statistic (95% CI)	Calibration/assessment of overfitting
Hambardzumyan[83]	MBDA	235	44[e]	NR	NR (sensitivity, specificity, PPV and NPV presented in *Table 32*)	NR
Markusse[85]	MBDA	84	NR	NR	0.77 (0.64 to 0.90)	NR
Prediction of radiographic joint damage (ΔSHS of > 5 at 2 years)						
Markusse[85]	MBDA	81	NR	NR	0.69 (0.453 to 0.93)	NR
Prediction of radiographic joint damage (ΔSHS of > 10 at 2 years)						
De Cock over 2 years[80]	ASPIRE CRP	74[a]	4	NR	0.70	O : E ratio:[b] 0.35
	ASPIRE ESR	74			0.60	0.42
	BeSt	73			0.60	0.27
	Syversen	73			0.25	0.08
	SWEFOT	74			0.41	0.20
	ESPOIR	73			0.35	0.31
Prediction of radiographic joint damage (ΔSHS of > 0.5 at 1 year)						
Heimans[84]	BeSt	537 (431 RA and 106 UA)	32	NR	0.56 (0.45 to 0.68)[f]	1.21
Markusse	MBDA	84	NR	NR	0.61 (0.48 to 0.73)	NR

Name of external validation study (submodels)	Clinical prediction model	Sample size (*n*)	Total number of observed events	Overall model fit (Nagelkerke's R^2)	Discrimination *c*-statistic (95% CI)	Calibration/assessment of overfitting
Prediction of radiographic joint damage (ΔSHS > 0.5 at 2 years)						
Markusse	MBDA	81			0.69 (0.56 to 0.81)	
Prediction of radiographic joint damage (≥ 5 Ratingen points at 3 years)						
de Punder[64]	BeSt ESPOIR	NR	NR	NR	Range 0.76–0.79 (no further information reported)	NR

NR, not reported; UA, undifferentiated arthritis.

a Sample sizes from the matrices supplied in the supplementary files of De Cock *et al.*[80] *N* varies according to the clinical prediction model that is being validated. This is likely to be because of missing baseline prognostic variables, whereby the included prognostic factors differ for the alternative models. Completed risk matrices were supplied for the > 2-year time point only; however, the allocation of individuals to cells of the risk matrices was presumed to be the same for the 'first year' time point, given that the baseline prognostic variables for these two evaluation periods are the same. This was confirmed with the authors in correspondence.

b Calculated from the provided risk matrices (see details in *Appendix 5*).

c Significant *p*-value indicates that the model does not fit the data.

d The reported value of 0.62 is likely to be a typographical error, as it is outside the range of the CI and is referred to in the text as being close to 0.5.

e Calculated by review authors from percentages supplied in the original report.

f Area under the curve reported for the mixed RA/undifferentiated arthritis population (80% of patients had RA).

The application of the BeSt model[79] was considered by Saevarsdottir *et al.*[73] using the SWEFOT data set. However, the presented results did not provide sufficient details to be considered to be informative to the current review, as no summary statistic of overall performance (e.g. the *c*-statistic) was provided.

Assessment of calibration

In order to assess the calibration of the models, the expected number of events according to each clinical prediction model was calculated in the external validation populations when possible (the De Cock *et al.*[80] and Heimans *et al.*[84] populations). Further details of the calculations used are provided in *Appendix 5*.

In the De Cock *et al.*[80] study, four events were observed in the first year of follow-up. However, the number of events predicted is substantially higher for all six of the considered clinical prediction models, leading to O : E ratios that are < 1. The O : E ratio ranged from 0.42 for ASPIRE ESR to 0.08 for Syversen *et al.*,[76] illustrating the poor calibration of the models in this population.

The calibration of the BeSt model[79] in the Heimans *et al.*[84] population appeared to be better, with an O : E of 1.21 (32 observed events, compared with 26.5 events predicted by the model). However, it was noted by the review authors that this external validation study used a different outcome definition of a > 0.5-unit increase in the SHS in order to classify the 32 events. Using the outcome definition of a SHS of > 5 (used in the BeSt model development), only one individual experienced rapid radiographic progression (RRP), which indicates a poor calibration (i.e. an O : E ratio of 0.04). Modification of the outcome definition by Heimans *et al.*[84] demonstrates that the BeSt model is not suitable for use in this population without recalibration.

In the case of the Granger *et al.*[82] validation study, it was not possible to compute the expected number of events. However, the study reported *p*-values from the Hosmer–Lemeshow test in order to assess calibration. This indicated that all models provided a poor fit to the data ($p < 0.01$) apart from the ASPIRE CRP model ($p = 0.25$). Contrary to what might be expected, the recalibrated ASPIRE CRP model provided a poorer calibration according to the Hosmer–Lemeshow test ($p < 0.01$) and also showed a higher value of the Bayesian information criterion (results shown in Granger *et al.*[82]), which raises questions as to the success of the calibration procedure.

Assessment of discrimination

The discriminatory ability of the models based on the *c*-statistic ranged from 0.344 to 0.675 for the Syversen and ASPIRE models, respectively, in the De Cock *et al.*[80] validation study assessed at 1 year. It is worth noting that the Syversen model[76] was developed in a cohort that included patients with up to 4 years' disease duration (mean 2.3. years' disease duration) and so was outside the 2-year limit used to define early RA in this assessment. This may partly explain the model's poor performance in the early RA external validation. The observed *c*-statistics ranged from 0.54 to 0.76 for the ASPIRE ESR and SONORA models, respectively, in the Granger *et al.* validation study.[82] The discrimination of BeSt[79] in the Heimans *et al.* external validation[84] (using a TSS of > 0.5 to define progression) was 0.56 (95% CI 0.45 to 0.68), showing poor discrimination with the CI including 0.5, despite calibration appearing to be reasonable in this population.

Assessment of heterogeneity

The predictive performance varied widely across the external validation populations. The two ASPIRE models provided the highest discriminatory ability in the De Cock *et al.* validation;[80] however, these models demonstrated the lowest discriminatory ability in the Granger *et al.*[82] validation. It has previously been demonstrated that the distribution of patient characteristics could substantially affect the discriminatory ability of a prediction model. When possible, variations in the populations that could be used to explain heterogeneity in the observed predictive performance were quantified by calculating the case mix of the population, using the mean and SD of the linear predictor/risk score as described in Debray *et al.*[40] Further details on how this was calculated are provided in *Appendix 5*, along with histograms of the risk scores for the models considered in De Cock *et al.*[80] and for the BeSt model considered in Heimans *et al.*[84] The mean

risk scores in the De Cock *et al.*[80] external validation population ranged from a 12.80% (SD 8.71%) predicted risk (PR) of progression, using the ASPIRE ESR model, to a 70.15% (SD 21.01%) PR of progression, using the Syversen model. This shows that, when evaluated in the same external population, the alternative risk models provide substantially different average risk predictions. The mean risk score for the BeSt model in the Heimans *et al.* external validation[84] population was 4.93% (SD 4.54%), compared with 20.59% (SD 16.83%) in the De Cock *et al.* validation population.[80] Although the De Cock *et al.*population had a larger case mix (with a greater SD of the linear predictor than obtained in the Heimans population), the observed discriminatory performance was lower. However, the calibration of the BeSt model in the De Cock *et al.* population was shown to be poor (O : E ratio of 0.27).

Although consideration of the case mix is of interest to illustrate the heterogeneity between alternative risk models, the case mix could not be computed for all of the external validation studies included in this review. There was also a small overall number of external validations. Further consideration of heterogeneity in discriminatory ability using metaregression was therefore not feasible.

Results of the evidence synthesis

In order to provide a comprehensive overview of the available evidence, a meta-analysis was considered for risk models that were externally validated in more than one study. For predicting RRP (SHS of > 5 in 1 year), three clinical prediction models (i.e. BeSt[79], ASPIRE CRP[78] and ASPIRE ESR[78]) were each externally validated in two studies (i.e. De Cock *et al.*[80] and Granger *et al.*[82]) that provided data in a suitable format. A meta-analysis was conducted using the *c*-statistic as a measure of discrimination. Although it would also be possible to synthesise other performance measures (e.g. the O : E ratio), other outcomes were not widely reported.

The predictive performance results are presented in *Table 11* for all external validations that considered RRP (SHS of > 5 in 1 year) as an outcome, along with the results of the FE and RE meta-analysis for the models that were assessed in more than one external validation study.

Of the models that were externally validated in more than one population, the BeSt model[79] shows the highest overall predictive performance (overall *c*-statistic 0.72, 95% CI 0.20 to 0.96), followed by ASPIRE ESR[78] and then ASPIRE CRP.[78] However, there is considerable uncertainty in the pooled estimates. For all three clinical prediction models, the 95% CI of the pooled estimate from the RE model contains 0.5, indicating that there is no confidence that the *c*-statistic is better than would be expected by chance. The 95% prediction intervals are not presented for the RE model as a result of the limited number of

TABLE 11 *c*-statistics and meta-analysis for models predicting RRP at 1 year

	External validation, *c*-statistic (95% CI)			Pooled estimate, mean (95%CI)	
Risk model	[a]De Cock *et al.*[80]	Granger *et al.*[82]	Markusse *et al.*[85]	RE	FE
BeSt	0.60 (0.31 to 0.83)	0.73 (0.65 to 0.81)		0.72 (0.20 to 0.96)	0.72 (0.63 to 0.79)
ASPIRE CRP	0.68 (0.38 to 0.88)	0.54 (0.45 to 0.64)		0.55 (0.13 to 0.91)	0.55 (0.46 to 0.64)
ASPIRE ESR	0.68 (0.38 to 0.88)	0.62 (0.54 to 0.69)		0.62 (0.44 to 0.78)	0.62 (0.55 to 0.69)
Syversen	0.34 (0.13 to 0.64)				
SWEFOT	0.52 (0.25 to 0.78)				
ESPOIR	0.35 (0.14 to 0.65)				
SONORA		0.76 (0.68 to 0.83)			
MBDA			0.77 (0.64 to 0.90)		

a De Cock. CI approximated from other information (see *Appendix 5*).

studies contributing to the analyses (therefore the prediction intervals returned by the model are the same as the CIs). The highest predictive performance in an individual study assessing the performance of models for the prediction of RRP at 1 year was shown by MBDA, with a *c*-statistic of 0.77 (95% CI 0.64 to 0.90), followed by SONORA with a *c*-statistic of 0.76 (95% CI 0.68 to 0.83); however, neither of these models were externally validated in more than one population (using the same outcome definition and presenting a suitable performance measure).

Consideration of results according to baseline disease severity

Given the limited reporting of the DAS28 at baseline in the included model development and external validation studies (see *Table 3*), it was not possible to draw conclusive inferences regarding the development or performance of clinical prediction models in populations with moderate versus severe disease activity based on the DAS28 at baseline.

Discussion

Twenty-two model development studies and one combined model development/external validation study describing 39 clinical prediction models for the assessment of prognosis in early RA patients were identified across a range of major outcomes (radiographic joint damage, HAQ score and DAS28). The large majority of these model development studies ($n = 16$) tested apparent performance only (TRIPOD statement type 1a). A total of six external validation studies (including the combined model development/external validation study) were identified that tested the performance of a total of eight previously developed clinical prediction models. All included external validation studies focused on radiographic joint damage outcomes.

Variation was observed in the methods used to develop the included clinical prediction models, such as those used to select or reject candidate predictors from the final model (e.g. informed by univariable analysis, statistical selection or clinical judgement) and handling of continuous predictors (e.g. division into categories). Some studies presented a 'matrix model', and so continuous variables were categorised to allow this presentation format, even though the categorisation of continuous covariates is generally not recommended for prognostic model development.[35,36] Model development studies also generally failed to assess interactions between predictors, including interactions with the treatment group, and so did not generate truly treatment-specific models. This is considered in further detail in *Chapter 5*.

There was also inconsistency in the measures of predictive performance reported from internal validation. The *c*-statistic was reported for 8 of the 23 model development studies, although sensitivity and specificity (eight studies), accuracy (seven studies) and PPV and/or NPV (12 studies) were also commonly reported. However, even if consistent approaches had been used for internal validation, comparing the performance of clinical prediction models that have been developed and internally validated in different populations would still be limited, as good discriminative ability in the population used to develop the model would be expected. External validation is required to provide an objective comparison.

Of the eight studies that reported predictive performance in internal validation using the *c*-statistic, the results were variable. The *c*-statistics for radiographic progression outcomes ranged between 0.63 (i.e. Degboé *et al.*,[66] predicting a ΔSHS of ≥ 5 at 1 year) and 0.87 (i.e. Houseman *et al.*,[72] predicting a ΔSHS of ≥ 10.5 at 8.2 years). The Houseman[72] models were notable in that they were among the few models that included MMP-3 in their final selection of predictors (MBDA also includes MMP-3). Unfortunately, the Houseman models[72] were assessed using apparent performance only and were not externally validated, and so it is not possible to verify the strong apparent predictive performance suggested in the study report. Furthermore, the Houseman model[72] included anti-CCP measured at the 8.2-year follow-up visit, which would bias the performance results relative to models that use only baseline information. Two studies

predicting the HAQ score reported *c*-statistics [0.78 (i.e. Dirven *et al.*,[67] HAQ score of ≥ 1 at 3 months) to 0.82 (i.e. Bansback *et al.*,[58] HAQ score of ≥ 1.5 at 5 years)], which also showed promising discrimination, albeit derived from internal validation.

Although the 39 included clinical prediction models present predictive performance results based on internal validation, 31 of these have not been externally validated. This could be largely explained by the fact that 21 of the clinical prediction models were not published in a useable format. Of the eight clinical prediction models that were externally validated, the majority were presented as risk matrices in the published report,[67,69,78,79] whereas two models were presented using the full model regression coefficients.[61,76] The SWEFOT[73] models were not presented in a useable format in the model development publication; however, the main SWEFOT model was considered in the De Cock *et al.*[80] external validation based on the results that are available in conference proceedings.[73] The SONORA model was externally validated by Granger *et al.*,[82] despite being available only in a non-useable format in abstracts.

For models that have been externally validated, predictive performance was observed to vary widely. The highest predictive performance of a clinical prediction model for the prediction of radiographic progression (ΔSHS of ≥ 5 at 1 year) in an individual external validation study was shown by MBDA, which was externally validated by Markusse *et al.*[85] (*c*-statistic 0.77, 95% CI 0.64 to 0.90), followed by SONORA, which was externally validated by Granger *et al.*[82] (*c*-statistic 0.76, 95% CI 0.68 to 0.83). However, neither of these models was externally validated for the prediction of radiographic progression in more than one population. The lowest predictive performance of a clinical prediction model for the prediction of radiographic progression (ΔSHS of ≥ 5 at 1 year) in an individual external validation study was shown by Syversen *et al.*,[76] which was externally validated by De Cock *et al.*[80] (*c*-statistic = 0.34) followed by ESPOIR (*c*-statistic = 0.35). For both of these models, the external validation results suggest a performance that is poorer than would be expected by chance (*c*-statistic < 0.5). However, the performance of ESPOIR was much more promising when externally validated by de Punder *et al.*,[64] in which *c*-statistics were reported to range from 0.76 to 0.79 using a different outcome definition (≥ 5 Ratingen points at 3 years).

Three clinical prediction models (i.e. ASPIRE CRP, ASPIRE ESR and BeSt) were externally validated in more than one population using the same outcome definition (ΔSHS of ≥ 5 at 1 year). The results of the RE meta-analysis implied that the most favourable performance across external validations was observed using the BeSt model (*c*-statistic 0.72, 95% CI 0.20 to 0.96), followed by ASPIRE ESR (*c*-statistic 0.62, 95% CI 0.44 to 0.78) and ASPIRE CRP (*c*-statistic 0.55, 95% CI 0.13 to 0.91). However, the favourable performance of BeSt was largely informed by the high *c*-statistic observed in the Granger *et al.* external validation,[82] and the BeSt model performed less favourably than either of the ASPIRE models in the De Cock *et al.* external validation.[80] There is considerable heterogeneity for all three models, with the wide CIs suggesting substantial uncertainty in the expected predictive performance in a new sample of patients. The 95% CIs of the pooled estimates contain 0.5 for all three clinical prediction models, indicating that there is limited confidence that the performance of the models is better than would be expected by chance.

Further external validations were identified in populations outside the scope of the assessment. These external validations were in populations with established RA. Vastesaeger *et al.*[78] tested the performance of their ASPIRE model[78] in data from the ATTRACT RCT {median disease duration of 8.4 years [interquartile range (IQR) 4.3–14.7 years]}. Lillegraven *et al.*[95] also tested the performance of the ASPIRE CRP,[78] BeSt[79] and SWEFOT[73] clinical prediction models in patients with established RA [median disease duration of 12 years (IQR 4–23 years)] and reported low predictive performance (*c*-statistics: ASPIRE, 0.59; BeSt, 0.65; and SWEFOT, 0.57).

No clinical prediction model performed consistently better than any other, and the current evidence therefore does not support the recommendation of one clinical prediction model over another. The inconsistent results generated by the clinical prediction models on external validation indicates that there is heterogeneity in the populations in which the models are being tested that is not explained by the currently proposed models.

However, in this assessment, it was not possible to explore the reasons for the observed heterogeneity, because of the small number of external validations.

The external validation of a clinical prediction model may not be straightforward if the treatment regimens used in the external validation population differ from those used in the original model development population. The authors of the external validation studies included in this review aimed to select the published clinical prediction matrices that provided the closest approximation to the treatment strategy in their external validation population. The issue of treatment practices changing over time, with the resulting differences in treatment between model development and external validation populations, was acknowledged by Steyerberg *et al.*[23] in their contribution to the PROGRESS series of publications. However, these authors also noted that it was important to consider whether or not existing models could be updated and their predictive performance improved by, for example, recalibration or the addition of new predictor variables. Moons *et al.*[31] also advocated the value of updating existing prediction models in order to improve their predictive performance in new settings or populations. Recalibration was considered only in the external validation by Granger *et al.*[82] However, there was evidence that recalibration may not have resulted in a better model fit.

In order to assess the comparative performance of the competing models more thoroughly, further external validations would be required. These should be conducted in clinically appropriate populations with early RA, previously untreated and with sufficient variation (or case mix) in the population to ensure that the results are generalisable to the target population.

Although further external validation would help to clarify whether or not selected models are likely to perform better than others, as previously discussed, there were limitations identified in the methods used to develop the clinical prediction models in many of the development studies. Limitations included the absence of potentially important candidate predictors, inconsistent selection procedures, incorrect handling of continuous predictors and failure to test for interactions between predictors. It is therefore likely that the most clinically useful prediction model would contain predictors from across more than one of the reviewed clinical prediction models and/or consider alternative handling of key predictive variables. Access to IPD would allow harmonisation (both in terms of model development and validation) beyond that which is possible in the current assessment, which considers only aggregate-level data.[96] Guidance on IPD meta-analyses of clinical prediction modelling studies, including the advantages and challenges of undertaking such projects, is given by Debray *et al.*[97] Methods for assessing clinical prediction models using IPD from multiple studies are also described by Pennells *et al.*[98] Although the provided reference focuses on the prediction of cardiovascular disease outcomes using time-to-event data, the key principles are relevant for the current review.

Therefore, despite the availability of a range of clinical prediction models, uncertainty still remains over the most appropriate clinical prediction model(s) for use in clinical practice. Future research efforts should focus on consolidating understanding from existing clinical prediction models and external validation studies, and ensuring that recommended practice for model development and reporting is adhered to.

The meta-analysis was limited by the small number of external validation studies available for analysis. The synthesised estimates are indicative of performance in the observed studies, but cannot be used to provide a definitive conclusion about the performance in future studies or to explore the reasons for the heterogeneity between studies. A bivariate meta-analysis of calibration and discrimination has also been proposed and could potentially be used to increase the precision of summary estimates and avoid the exclusion of studies for which relevant estimates are missing.[99] However, this was not considered in this assessment because of the other described limitations of the evidence base.

Review 1 conclusions

Despite the availability of a range of clinical prediction models, uncertainty still remains over the most appropriate clinical prediction model(s) for use in clinical practice. In order to assess the comparative performance of the competing models more thoroughly, further external validations would be required. However, limitations were observed in the methods used to develop the clinical prediction models. It is likely that the most clinically useful prediction model would contain predictors from across more than one of the reviewed clinical prediction models and/or consider alternative handling of key predictive variables.

Chapter 5 Results: review 2

Quantity of research available

Only one of the clinical prediction models involving multiple treatments that were reported in review 1 investigated potential interactions between treatments and predictor variables.[79]

The study selection process for review 2 is depicted in *Figure 7*. A total of 12 studies were included,[78,100–111] two of which used the same data set.[78,100]

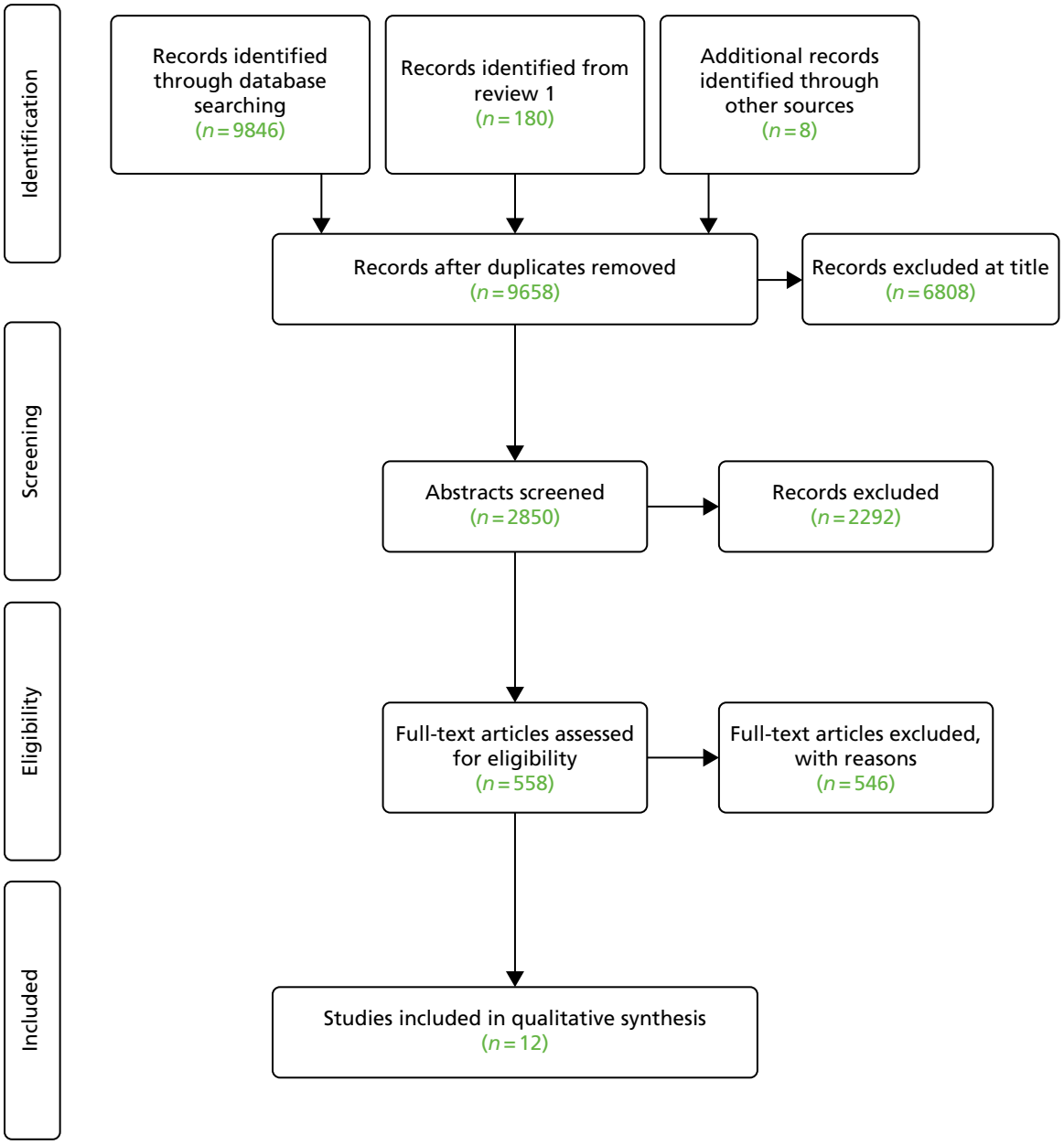

FIGURE 7 Review 2 study selection represented as a PRISMA flow diagram.[55]

It was stated in the final protocol that any potential overlap would be highlighted between this report and the National Institute for Health Research (NIHR) HTA Technology Assessment Review (TAR) report number 14/16/01. One study included in review 2 (i.e. Taylor *et al.*[101]) was also included in the HTA TAR report number 14/16/01. This study examined the effect of baseline synovial vascularity assessed by PDUS on radiographic progression at 54 weeks by MTX versus MTX and IFX. Other studies in the NIHR HTA TAR report number 14/16/01 were screened for relevance to the current review, but were excluded for not examining an early RA population and/or not examining the interaction between baseline patient and/or disease characteristics and treatments.

A summary of the 12 included studies that are used to assess the prediction of treatment response by patient and/or disease characteristics is presented in *Table 12*. All included studies were post hoc subgroup analyses of RCTs.[78,100–111] The geographical locations of the studies included the Netherlands,[103] the USA,[105,110] Finland,[106] Italy,[107] Germany[108] and the UK,[101,109] with three studies examining data from two multinational trials[78,100,104] and one study not reporting location.[102] Sample sizes ranged from 24 to 1004 participants; most studies were funded by the pharmaceutical industry,[78,100–105,107,110] two studies reported funding from local or national health-care agencies[106,109] and one study did not report the funding source.[108]

Overall quality of research available

All included studies were rated as being at a moderate risk of bias, according to the QUIPS assessment tool[54] (*Table 13*). Generally, most studies were rated as being at a moderate risk of bias for study participation. This was mainly because most studies did not report the source of the target population and the methods used to recruit patients to the study, with many not reporting or partially reporting whether or not there was adequate participation in the study. Most studies reported the recruitment period, inclusion and exclusion criteria and baseline characteristics.

The majority of studies were also rated as being at a moderate risk of bias for study attrition. This was mainly because most studies did not report the proportion of the baseline sample that provided data for analysis or what attempts were made to collect information on participants who dropped out. Most studies did not report, or partially reported, the key characteristics for participants who dropped out or the comparative characteristics of those who dropped out and those who provided follow-up data. However, reasons for the loss of follow-up data were typically reported.

Most studies were also rated as being at a moderate risk of bias for prognostic factor measurement. This was mainly because of a lack of clarity or reporting surrounding the proportion of data on the prognostic factor that was available for analysis and the method used for dealing with missing data in most studies. The method and setting of prognostic factor measurement was reported by approximately half of the included studies, and most studies reported a definition and also valid and reliable measurement of the prognostic factor.

Most studies were rated as being at a low risk of bias for outcome measurement. This was mainly attributable to most of the studies reporting a clear definition of the outcome, valid and reliable measurement of the outcome and the method and setting of the outcome being the same for all participants.

Study confounding was also rated as being at a moderate risk of bias for most studies. This was mainly attributable to a lack of reporting or partial reporting among the majority of studies on whether or not important confounders were measured and the definition and valid and reliable measurement of these, and also the method and setting of confounding measurement and whether or not important confounders were accounted for in the study design and analysis.

TABLE 12 Characteristics of the included primary studies

First author (year of publication), name of trial or cohort (if relevant)	Characteristics						
	Study design	Geographical location and period of data collection	Key eligibility criteria	Maximum length of follow-up	Sample size (number of participants)	Assessment of risk of bias (low/moderate/high)[a]	Funding
Garnero (2002)[102]	Cohort study [efficacy analyses of patients included in a RCT (i.e. Bathon 2000[112])]	Unclear location 1997–9	Early active RA for ≤ 3 years with ≥ 10 swollen joints, ≥ 12 tender joints, aged ≥ 18 years, diagnosed in accordance with the 1987 revised ACR criteria, RF+, serum CRP level of ≥ 2.0 mg/dl, three or more radiographic erosions of the hands, wrists or feet	12 months	116	Moderate	Immunex (Seattle, WA, USA)
Heimans (2013)[103] BeSt	RCT (post hoc analyses)	The Netherlands 2000–2 (recruitment)	Early active RA (1987 revised ACR criteria); disease duration of ≤ 2 years; active disease (≥ 6/66 swollen joints, ≥ 6/68 tender joints, and either an ESR of 28 mm/hour or a global health score of 20 mm on a 0- to 100-mm visual analogue scale), aged ≥ 18 years[b,c]	10 years	484 patients (sample size at 8 years' follow-up; initial cohort = 508 patients)	Moderate	Dutch College of Health Insurance Companies; Centocor Inc. (Horsham, PA, USA); and Schering-Plough (Kenilworth, NJ, USA)
Huizinga (2015)[104] AVERT	Post hoc analysis of RCT (phase 3b, multicentre, randomised, active-controlled study)	Multicentre – 72 worldwide sites, including North America, South America, Europe and the rest of the world NR	Adults (≥ 18 years old) with active clinical synovitis of ≥ 2 joints for ≥ 8 weeks, persistent symptoms for ≤ 2 years, DAS28-CRP of ≥ 3.2 and anti-CCP-2 anti-body positivity, MTX naive or received MTX (≤ 10 mg/week) for ≤ 4 weeks with no MTX for 1 month prior to enrolment	18 months	511 patients enrolled; 351 patients randomised	Moderate	Bristol-Myers Squibb (New York City, NY, USA)
Maska (2012)[105] TEAR	RCT (subgroup analyses)	USA NR	Early active RA (1987 revised ACR criteria; disease duration of < 3 years); aged > 18 years, active disease (≥ 4 swollen joints and ≥ 4 tender joints based on DAS28-joint count), RF+ or ACPA+, or ≥ 2 erosions on radiographs of the hands/wrists/feet if RF– or ACPA–	2 years (102 weeks)	A total of 412 patients (with available serum cotinine data at baseline, week 48 and week 102 from study sample; *n* = 755) included in the analyses	Moderate	Amgen (Thousand Oaks, CA, USA; provided ETN and placebo); Barr pharmaceuticals (Montvale, NJ, USA; provided MTX); Pharmacia (New Jersey, USA) (SSZ and placebo); and NIH planning grant (PI: Moreland; 1 R34 AR055122) from NIAMS for the TEAR study
Mustila (2011)[106] FIN-RACo	RCT	Finland (18 centres) 1993–5 (recruitment)	Clinically active RA (1987 revised ACR criteria), symptom duration of < 2 years, DMARD naive	5 years	129 (of 199 randomised – completing 5 years' follow-up, with clinical and radiographic data)	Moderate	Competitive research funding of the Pirkanmaa Hospital District, Tampere University Hospital (Tampere, Finland)

continued

TABLE 12 Characteristics of the included primary studies (*continued*)

First author (year of publication), name of trial or cohort (if relevant)	Characteristics						
	Study design	Geographical location and period of data collection	Key eligibility criteria	Maximum length of follow-up	Sample size (number of participants)	Assessment of risk of bias (low/moderate/high)[a]	Funding
Pasero (1996)[107]	RCT (subgroup of patients with or without joint erosions)	Italy 1991–3 (recruitment)	Early active RA; disease duration of at least 6 months, but ≤ 4 years; aged 18–65 years, fulfilling 4/7 1987 revised ACR criteria and in Steinbrocker functional class I, previously untreated or treated with a maximum of only one DMARD (an antimalarial agent or auranofin), discontinued because of side effects or lack of efficacy, ESR > 30 mm/hour, morning stiffness for ≥ 45 minutes, and three or more swollen and tender joints, including two or more hand joints	12 months	361 patients enrolled; 340 patients available for ITT analysis (complete set of radiographs, available for *n* = 284 patients)	Moderate	Sandoz PF (Corso Verona, Italy)
Rau (1998)[108]	Randomised, double-blind, parallel-group trial	Germany (two centres) NR	Active disease RA (presence of three of: 1. an ESR of > 20 mm/hour in men and > 30 mm/hour in women 2. morning stiffness for ≥ 1 hour 3. six or more swollen joints 4. nine or more tender joints) A disease duration of ≥ 4 months, with erosive disease Patients with advanced radiographic changes (Larsen stages III–V) in any joint, prior treatment with MTX or GSTM, treatment with any other DMARD during the previous 3 months, and intra-articular steroid injection within the previous 4 weeks were excluded	12 months	174 patients enrolled (complete set of radiographs, available for *n* = 152 patients)	Moderate	NR

First author (year of publication), name of trial or cohort (if relevant)	Characteristics						
	Study design	Geographical location and period of data collection	Key eligibility criteria	Maximum length of follow-up	Sample size (number of participants)	Assessment of risk of bias (low/moderate/high)[a]	Funding
Seegobin (2014)[109] CARDERA	RCT	UK (42 centres) 2000–4[d]	Early active RA (1987 ACR criteria, < 2 years' duration), aged ≥ 18 years, with three of three or more swollen joints, six or more tender joints, ≥ 45 minutes' morning stiffness, ESR of ≥ 28 mm/hour	2 years	431 (from 467 recruited – with evaluable baseline sera)	Moderate	Arthritis Research UK and NIHR under its Research for Patient Benefit Programme
Smolen (2006)[100] Vastesaeger (2009)[78] ASPIRE	Exploratory analysis of RCT data	Multicentre study (122 centres in Europe – Austria, the Netherlands, Germany, the UK and the USA) 2000–2 (recruitment)[e]	Early active RA (1987 revised ACR criteria); age 18–75 years, persistent synovitis for ≥ 3 months and ≤ 3 years, ≥ 10 swollen joints, ≥ 12 tender joints, one or more of RF, serum CRP level of ≥ 2.0 mg/dl, radiographic erosions of the hands or feet. No prior treatment with MTX, no other DMARDs within 4 weeks of study entry	54 weeks	1004	Moderate	Centocor Inc. (Horsham, PA, USA; subsidiary of Johnson & Johnson) and Schering-Plough (Kenilworth, NJ, USA)
Sokolove (2016)[110] AMPLE	Exploratory analysis of RCT	USA 2009–12	bDMARD-naive patients with active RA (1987 revised ACR criteria) and an inadequate response to MTX; a DAS28-CRP of ≥ 3.2 and a history of ACPA+ or RF+ and/or elevated ESR or CRP levels,[f] aged > 18 years and disease duration of ≤ 5 years	729 days (2 years approximately)	573 patients completed 2 years, with 508 who had serum samples at baseline	Moderate	Bristol-Myers Squibb (New York City, NY, USA)

continued

TABLE 12 Characteristics of the included primary studies (*continued*)

First author (year of publication), name of trial or cohort (if relevant)	Characteristics						
	Study design	Geographical location and period of data collection	Key eligibility criteria	Maximum length of follow-up	Sample size (number of participants)	Assessment of risk of bias (low/moderate/high)[a]	Funding
Taylor (2004)[101]	RCT	UK NR	RA diagnosis (1987 revised ACR criteria), symptoms for 6 months to 3 years, two or more swollen MCP joints despite MTX, IgM RF+, receiving MTX at a stable dose of 12.5–17.5 mg/week for ≤ 4 weeks prior to screening, either not taking corticosteroids or receiving a stable dose of ≥ 10 mg of prednisolone per day for ≥ 4 weeks, plus either: 1. erosion of one or fewer MCP joints on plain radiography of GSUS 2. erosions of two or fewer MCP joints with a strong PDUS vascular signal	54 weeks	24	Moderate	Centocor (Horsham, PA, USA; supplied study drug, had a role in analysis and interpretation) and the Rheumatoid Arthritis Campaign

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; AMPLE, abatacept vs. adalimumab in biologic-naive RA patients with background MTX; AVERT, A Very Early Rehabilitation Trial; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; DMARD, disease-modifying antirheumatic drug; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; GSTM, gold sodium thiomalate; GSUS, grey scale ultrasound; IgM, immunoglobulin M; MCP, metacarpophalangeal; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH, National Institutes for Health; NR, not reported; PI, principal investigator; TEAR, Treatment of Early Aggressive Rheumatoid arthritis.

a According to the QUIPS assessment tool,[54] this will be summarised in more detail in *Overall quality of research available* and *Table 13*.

b From van der Kooij *et al.*[113]

c From Goekoop-Ruiterman *et al.*[89]

d From Choy *et al.*[114]

e From St Clair *et al.*[87]

f From Weinblatt *et al.*[115]

TABLE 13 Risk of bias of included primary studies – QUIPS summary ratings

First author (year of publication), name of trial or cohort (if relevant)	Risk of bias of						
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and presentation	Overall risk of bias summary
Garnero (2002)[102]	High	Moderate	Moderate	Low	Moderate	High	Moderate
Heimans (2013)[103]	Low	Moderate	Low	Moderate	Moderate to low	Moderate	Moderate
BeSt							
Huizinga (2015)[104]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate[a]
AVERT							
Maska (2012)[105]	Low	Moderate	Moderate	Low	Moderate to low	Low	Moderate
TEAR							
Mustila (2011)[106]	Moderate	Moderate	Low	Low	High	Moderate	Moderate
FIN-RACo							
Pasero (1996)[107]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Rau (1998)[108]	High	Low	Moderate	Low	Moderate	Moderate	Moderate
Seegobin (2014)[109]	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
CARDERA							
Smolen (2006)[100]	Moderate	High	Moderate	Low	Moderate	Moderate	Moderate
ASPIRE							
Sokolove (2015)[110]	Moderate to high	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
AMPLE							
Taylor (2004)[101]	Moderate	Moderate	Moderate to low	Low	Moderate to high	Moderate	Moderate
Vastesaeger (2009)[78]	Moderate	High	Moderate	Low	Moderate	High	Moderate
ASPIRE							

AMPLE, abatacept vs. adalimumab in biologic-naive RA patients with background MTX; AVERT, Assessing Very Early Rheumatoid arthritis Treatment; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; TEAR, Treatment of Early Aggressive Rheumatoid arthritis.

a Based on Emery *et al.*[116]

Most studies were also rated as being at a moderate risk of bias for statistical analysis. This was mainly because of uncertainty over whether or not the presentation of the analytical strategy and model development strategy and the avoidance of selective reporting of results were adequate, because of a lack of a clear description in most studies.

Treatments, baseline variables and outcomes examined of the included studies

Table 14 summarises the treatments, patient and/or disease characteristics and outcomes examined. Numerous treatment comparisons were made, including:

- ETN versus MTX[102]
- sequential monotherapy with initial MTX versus step-up monotherapy with initial MTX versus MTX and SSZ and tapered prednisone versus MTX and IFX[103]
- ABT (subcutaneous administration) and MTX versus ABT (subcutaneous administration) versus MTX[104]
- MTX and ETN immediate therapy versus MTX and SSZ and HCQ immediate therapy versus MTX and ETN step-up therapy versus MTX and SSZ and HCQ step-up therapy[105]
- MTX and HCQ and SSZ in a treat-to-target (TTT) regime versus cDMARD sequential monotherapy in a TTT regime, starting with SSZ[106]
- ciclosporin A (CsA) versus cDMARDs[107]
- MTX versus gold sodium thiomalate (GSTM)[108]
- MTX versus MTX and CsA versus MTX and prednisolone versus MTX and CsA and prednisolone (in a factorial design)[109]
- MTX versus MTX and IFX (3 mg/kg or 6 mg/kg)[78,100]
- MTX and ABT (subcutaneous administration) versus MTX and ADA (subcutaneous administration),[110] and
- MTX versus MTX and IFX.[101]

Eligible baseline variables were ACPA status,[104,106,109,110] smoking status,[105] erosions,[100,107] RF status,[100,111] CRP level,[100–102] ESR,[100,108] SJC,[100] BMI[103] and vascularity of synovium detected using PDUS.[101]

Eligible outcomes were erosions/radiographic progression,[100–102,106–109] disease activity,[105,109] physical function,[109,110] remission[103,110] and a DAS of > 2.4.[103] Four studies assessed outcomes at 6 months,[105,108–110] 11 studies assessed outcomes at 1 year,[100–103,106–110] one study assessed outcomes at 18 months,[109] four studies assessed outcomes at 2 years,[105,106,109,110] and one study assessed outcomes at 3, 4 and 5 years.[106]

Description of population characteristics

The key population characteristics are summarised in *Table 15* (and additional population characteristics are summarised in *Appendix 9, Table 34*).

The majority of included studies used the 1987 revised ACR criteria for RA diagnosis.[100–103,105–107,109,110] One study did not report the diagnosis criteria[104] and one study reported using the ACR case criteria.[108] Five studies defined early RA as being active RA or the presence of symptoms for a duration of < 2 years,[103,104,106,109,110] four studies defined early RA as being active RA or the presence of symptoms for a duration of < 3 years[100–102,105] and two studies used other definitions (active RA for ≥ 6 months but ≤ 4 years,[107] or by radiographic definition, i.e. patients without advanced disease[108]); in all cases, baseline mean/median disease/symptom duration met the inclusion criterion for early RA (i.e. being within 2 years of the onset of symptoms) for this review.

TABLE 14 Treatments, baseline variables and outcomes of included primary studies

First author (year of publication), name of trial or cohort (if relevant)	Treatment comparison	Variable(s)	Measurement and timing of variable	Outcomes	Measurement and timing of outcomes	Assessment time of outcome measurement
Garnero (2002)[102]	ETN MTX	CRP level	Baseline (high levels of CRP were defined as those in the upper tertile of the RA population). No further details reported	Erosion and radiographic progression	Change from baseline in SHS erosion score and SHS total score at 12 months	1 year
Heimans (2013)[103] BeSt	Sequential monotherapy (initial MTX) Step-up combination therapy (initial MTX) Combination therapy MTX and SSZ and tapered prednisone Combination therapy MTX and IFX	BMI	Calculated from height and weight, as assessed at baseline by a research nurse. Dichotomised to < 25 kg/m^2 and ≥ 25 kg/m^2	Treatment response	A DAS of > 2.4, failed response to treatment, measured in the first 3 months of treatment and at year 1	1 year
Huizinga (2015)[104] AVERT	ABT (s.c. administration) and MTX ABT (s.c. administration) and MTX	ACPA status (anti-CCP2 status)	Measured at baseline; no further details reported	Remission	A DAS28 of < 2.6 at 12 months	1 year
Maska (2012)[105] TEAR	MTX and ETN immediate therapy MTX and SSZ and HCQ immediate therapy MTX and ETN step-up therapy MTX and SSZ and HCQ step-up therapy	Smoking status	Measured at baseline and week 48: smokers = detectable (serum) cotinine level of > 5 ng/ml at both visits; non-smokers = undetectable cotinine levels at both baseline and week 48 visits	Disease activity	Mean DAS28 at 48–102 weeks Mean DAS28 (absolute) at 24 weeks, 48 weeks and 102 weeks	1–2 years 6 months 1 year 2 years

continued

TABLE 14 Treatments, baseline variables and outcomes of included primary studies (*continued*)

First author (year of publication), name of trial or cohort (if relevant)	Treatment comparison	Variable(s)	Measurement and timing of variable	Outcomes	Measurement and timing of outcomes	Assessment time of outcome measurement
Mustila (2011)[106] FIN-RACo	MTX and HCQ and SSZ in a TTT regime; cDMARD sequential monotherapy in a TTT regime (starting with SSZ)	ACPA status	ACPAs were determined from a serum sample drawn at baseline and at 1, 2 and 5 years; a cut-off value of 25 U/ml. ACPA results of < 25 U/ml were defined as negative	Erosion by radiographic progression	Larsen score obtained from once-yearly radiographs of the hands and feet by one experienced radiologist, blinded to clinical data	1, 2, 3, 4 and 5 years
Pasero (1996)[107]	CsA Conventional DMARDs	Erosions	Presence or absence of erosions at baseline, as determined by the Larsen–Dale method	Erosions/ radiographic progression	Progression in eroded joint count (PEJC) and progression in damage score calculated as the difference in eroded joint count and damage score from baseline using the Larsen–Dale method	12 months
Rau (1998)[108]	MTX GSTM	RF ESR CRP level	Baseline, after 6 and 12 months Baseline, after 1, 3, 6, 9 and 12 months Baseline, after 1, 3, 6, 9 and 12 months	Radiographic progression	Rau-modified Sharp/Larsen score	6 and 12 months
Seegobin (2014)[109] CARDERA	MTX monotherapy MTX and CsA MTX and prednisolone MTX and CsA and prednisolone (in a factorial design)	ACPA status	ACPA status (positive or negative), evaluated using an anti-CCP2 test with a cut-off point of > 5 units/ml taken as positive	Radiological progression Disease activity Physical function	Onset of new erosions at 24 months and modified Larsen scores every 6 months DAS28 every 6 months HAQ score every 6 months	6, 12, 18 and 24 months
Smolen (2006)[100] ASPIRE	MTX MTX and IFX (3 mg/kg or 6 mg/kg)	ESR, CRP level, erosions, RF status, SJC	Baseline ESR, CRP level and radiographic erosions of hands and feet (assessed at time of study entry) using SHS	Radiographic progression	Worsening of radiographic joint damage (change in the SHS of > 0) from baseline to week 54	Week 54

First author (year of publication), name of trial or cohort (if relevant)	Treatment comparison	Variable(s)	Measurement and timing of variable	Outcomes	Measurement and timing of outcomes	Assessment time of outcome measurement
Sokolove (2016)[110] AMPLE	MTX and ABT (s.c. administration) MTX and ADA (s.c. administration)	ACPA status (anti-CCP2 status)	Baseline anti-CCP2 anti-body status (positive/negative) was determined using an anti-CCP2 IgG ELISA. Patients with a baseline anti-CCP2 IgG concentration of ≥ 25 AU/ml were considered to be positive and were further divided into equal quartiles according to concentration [Q1–Q4 (highest concentration)] Measurement assessed at various time points up to day 729	Disease activity Physical function	Adjusted mean change from baseline in DAS28-CRP at various time points up to 729 days (2 years) – data extracted only for 6 months, 1 year and 2 years Adjusted mean change from baseline in HAQ-DI score at various time points up to 729 days (2 years)	Various time points up to 729 days (2 years) – data extracted only for 6 months, 1 year and 2 years
Taylor (2004)[101]	MTX MTX and IFX	Baseline synovial vascularity	MCP joints scanned in PD mode (14 MHz) and images demonstrating maximal synovial vascularity were scored by calculating the sum of the individual joint scores, which consisted of the number of colour Doppler pixels in a defined region of interest for each joint. Taken at baseline and week 18	Radiographic progression	Progression in total SHS scored by blinded, independent observers from radiographs taken at baseline and at week 24 (mean of the scores of the two independent assessors). Change from baseline to week 54 calculated	Week 54
Vastesaeger (2009)[78] ASPIRE	MTX MTX and IFX (3 mg/kg or 6 mg/kg)	ESR, CRP level, RF status, SJC	ESR assessed at baseline via the Westergren method; CRP level measured at baseline by nephelometry; RF status evaluated from baseline samples evaluated at the central laboratory; 66-joint SJC taken at baseline (although 28-joint SJC used)	Radiographic progression	Differences between treatment groups in mean van der Waerden normal scores of the change of ≥ 5 units/year in total SHS	Week 54

AMPLE, abatacept vs. adalimumab in biologic-naive RA patients with background MTX; AVERT, Assessing Very Early Rheumatoid arthritis Treatment; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; CCP2, cyclic citrullinated peptide-2; CsA, ciclosporin A; ELISA, enzyme-linked immunosorbent assay; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; GSTM, gold sodium thiomalate; HAQ-DI, Health Assessment Questionnaire – disability index; IgG, immunoglobulin G; MCP, metacarpophalangeal; PD, power Doppler; s.c., subcutaneous; TEAR, Treatment of Early Aggressive Rheumatoid arthritis; TTT, treat to target.

TABLE 15 Key population characteristics of included primary studies at baseline

First author (year), name of trial or cohort (if relevant)	Diagnosis of RA	Definition of early RA	Group/arm	Mean/median duration (months) of symptoms/ disease at baseline	Mean/median DAS28 at baseline	Treatment history and current treatments
Garnero (2002)[102]	1987 revised ACR criteria	Active RA for ≤ 3 years	All participants	12 (SD 12)[a]	NR	Not previously treated with MTX. DMARDs, including HCQ and SSZ, were discontinued at least 4 weeks before study entry; stable doses of corticosteroids (≤ 10 mg of prednisone or equivalent) and NSAIDs were permitted. A total of 46% of participants in the MTX arm, 39% in the ETN (10 mg) arm and 40% in the ETN (25 mg) arm had previously used DMARDs, with the mean (SD) number of DMARDs being 0.6 (0.7), 0.5 (0.7) and 0.5 (0.7), respectively; 80%, 76% and 86%, respectively, using concomitant NSAIDs at baseline; and 41%, 42% and 39%, respectively, using concomitant glucocorticoids at baseline[b]
Heimans (2013)[103] BeSt	1987 revised ACR criteria	Active RA for ≤ 2 years	All participants	NR	DAS: 4.4 (SD 0.9)[c]	No prior DMARDs
			A BMI of < 25 kg/m^2	5.3 (IQR 3.0–13.2)[d]	DAS: 4.4 (SD 0.8)	
			A BMI of ≥ 25 kg/m^2	5.3 (IQR 3.0–10.8)[d]	DAS: 4.4 (SD 0.9)	
			Sequential monotherapy	5.3 (IQR 3.2–12.5)[d]	DAS: 4.5 (SD 0.9)	
			Step-up combination therapy	6.0 (IQR 3.2–12.9)[d]	DAS: 4.5 (SD 0.8)	
			MTX + SSZ + tapered prednisone	5.3 (IQR 3.5–12.2)[d]	DAS: 4.4 (SD 0.9)	
			MTX + IFX	5.3 (IQR 3.0–10.6)[d]	DAS: 4.3 (SD 0.9)	

First author (year), name of trial or cohort (if relevant)	Diagnosis of RA	Definition of early RA	Group/arm	Mean/median duration (months) of symptoms/ disease at baseline	Mean/median DAS28 at baseline	Treatment history and current treatments
Huizinga (2015)[104] AVERT	NR	Onset of symptoms for ≤ 2 years	All participants	6.72 (SD 6.0)[d,e]	5.4 (SD 1.2)[e,f]	MTX naive or received MTX (≤ 10 mg/ week) for ≤ 4 weeks with no MTX for 1 month prior to enrolment. Patients receiving oral corticosteroids were required to be on a stable dose (i.e. ≤ 10 mg/day for ≥ 4 weeks) at initiation and to maintain that dose until month 12
			ABT (s.c. administration) and MTX	6.96 (SD 6.0)[d,e]	5.5 (SD 1.3)[e,f]	
			ABT (s.c. administration)	7.08 (SD 6.24)[d,e]	5.5 (SD 1.1)[e,f]	
			MTX	6.0 (SD 5.88)[d,e]	5.3 (SD 1.3)[e,f]	
Maska (2012)[105] TEAR	1987 revised ACR criteria	Disease duration for < 3 years	All participants (with serum cotinine at baseline and week 48)	3.7 (SD 6.6)[a]	5.8 (1.1)	bDMARD naive[g] On stable corticosteroid treatment and < 10 mg/day of prednisone or equivalent or on a stable dose of NSAIDs Prior MTX use in 157 out of 755 patients (21%)[g]
			Current smokers	3.4 (SD 6.9)[a]	5.8 (SD 1.1)	
			Non-smokers	3.8 (SD 6.5)[a]	5.8 (SD 1.0)	
Mustila (2011)[106] FIN-RACo	1987 revised ACR criteria	Symptom duration for < 2 years	All participants	7.7 (SD 5.0)[a,c]	7.7 (SD 5.0)[c]	DMARD naive
			ACPA+	NR	NR	
			ACPA–	NR	NR	
			MTX and HCQ and SSZ in a TTT regime	7.3 (SD 4.7)[a]	5.5 (SD 1.0)	
			cDMARD sequential monotherapy in a TTT regime (starting with SSZ)	8.2 (SD 5.2)[a]	5.6 (SD 1.1)	

continued

TABLE 15 Key population characteristics of included primary studies at baseline (*continued*)

First author (year), name of trial or cohort (if relevant)	Diagnosis of RA	Definition of early RA	Group/arm	Mean/median duration (months) of symptoms/ disease at baseline	Mean/median DAS28 at baseline	Treatment history and current treatments
Pasero (1996)[107]	1987 revised ACR criteria	Active RA, a duration of at least 6 months but ≤ 4 years	All participants	1.4 (SD 1.1)[a,c]	NR	DMARD naive or treated with a maximum of only one DMARD (an antimalarial agent or auranofin)
			Patients with joint erosions at baseline	NR	NR	
			Patients without joint erosions at baseline	NR	NR	94 out of 141 patients receiving CsA and 103 out of 143 patients in the radiologically evaluable ITT subset had previously used NSAIDs; 56 out of 141 and 52 out of 143, respectively, for corticosteroids; 43 out of 141 and 31 out of 143, respectively, for antimalarial agents or auranofin
			CsA arm	1.4 (SD 1.2)[a]	NR	
			Other cDMARDs arm	1.3 (SD 1.1)[a]	NR	
Rau (1998)[108]	ACR case criteria	By radiographic definition: patients with advanced disease (higher than Larsen grade III) were excluded	All patients	NR	NR	No prior treatment with MTX or GSTM, no treatment with any other DMARD during the previous 3 months, no intra-articular steroid injection within the previous 4 weeks
			MTX	11.5[a,h]	NR	
			GSTM	11.2[a,h]	NR	
Seegobin (2014)[109] CARDERA	1987 ACR criteria	Active RA for < 2 years	All participants	4.0 (SD 5.1)[a,c]	5.8 (SD 1.3)[c]	A total of 65 patients (14% of the trial population) had previously received DMARDs
			ACPA+	2.00 (IQR 0.00–5.00)[a]	5.72 (IQR 4.91–6.73)	
			ACPA–	1.00 (IQR 0.00–4.00)[a]	5.96 (IQR 4.92–6.85)	
			MTX monotherapy[i]	2.7 (SD 3.8)[a]	5.8 (SD 1.2)	
			CsA and MTX	4.2 (SD 5.7)[a]	5.9 (SD 1.3)	
			Prednisolone and MTX	5.1 (SD 5.8)[a]	5.8 (SD 1.4)	
			Triple therapy	3.9 (SD 5.2)[a]	5.6 (SD 1.3)	

First author (year), name of trial or cohort (if relevant)	Diagnosis of RA	Definition of early RA	Group/arm	Mean/median duration (months) of symptoms/ disease at baseline	Mean/median DAS28 at baseline	Treatment history and current treatments
Smolen (2006)[100]	1987 revised ACR criteria	Active RA < 3 years	All participants	10.4 (SD 8.8)[a,c]	6.7 (SD 1.0)[d]	No prior treatment with MTX, no other DMARDs within 4 weeks of study entry
Vastesaeger (2009)[78]			MTX	10.8 (SD 8.4)[a]	6.7 (SD 1.0)[j]	
ASPIRE			IFX (all doses)	10.2 (SD 9.0)[a,c]	6.7 (SD 1.0)[c]	
			MTX + IFX 3mg/kg	9.6 (SD 8.4)[a]	6.6 (SD 1.1)[j]	
			MTX + IFX 6mg/kg	10.8 (SD 9.6)[a]	6.7 (SD 1.0)[j]	
Sokolove (2015)[110]	1987 revised ACR criteria	Disease duration of ≤ 2 years	All patients	NR	NR	bDMARD-naive patients with an inadequate response to MTX
AMPLE			Anti-CCP2	ABT: 12.0 (range 1.2–55.2)[a,k]	ABT: 5.5 (range 2.5–7.4)[j]	
				ADA: 15.6 (range 0.0–56.4)[a,k]	ADA: 5.3 (range 3.0–7.3)[k]	
			Anti-CCP2+; Q1 28–235 AU/ml	ABT: 21.6 (range 2.4–54.0)[a,k]	ABT: 5.0 (range 3.1–7.6)[j]	
				ADA: 19.2 (range 1.2–61.2)[a,k]	ADA: 5.5 (range 3.1–7.3)[k]	
			Anti-CCP2+; Q2 236–609 AU/ml	ABT: 20.4 (range 1.2–61.2)[a,k]	ABT: 5.6 (range 3.5–7.6)[j]	
				ADA: 14.4 (range 1.2–54.0)[a,k]	ADA: 6.0 (range 2.8–7.4)[k]	
			Anti-CCP2+; Q3 613–1046 AU/ml	ABT: 21.6 (range 1.2–57.6)[a,k]	ABT: 5.5 (range 2.8–8.1)[k]	
				ADA: 20.4 (range 1.2–61.2)[a,k]	ADA: 5.7 (range 3.7–7.9)[k]	
			Anti-CCP2+; Q4 1060–4894 AU/ml	ABT: 24.0 (range 1.2–57.6)[a,k]	ABT: 6.0 (range 2.7–7.8)[j]	
				ADA: 16.8 (range 0.0–60.0)[a,k]	ADA: 5.3 (range 1.7–7.8)[j]	

continued

TABLE 15 Key population characteristics of included primary studies at baseline (*continued*)

First author (year), name of trial or cohort (if relevant)	Diagnosis of RA	Definition of early RA	Group/arm	Mean/median duration (months) of symptoms/ disease at baseline	Mean/median DAS28 at baseline	Treatment history and current treatments
Taylor (2004)[101]	1987 revised ACR criteria	6 months to ≤ 3 years	All	17.9 (SD 7.6)[a,c]	5.3 (SD 1.1)[c]	Receiving MTX at a stable dose of 12.5–17.5 mg/week for ≤ 4 weeks prior to screening, either not taking corticosteroids or receiving a stable dose of ≥ 10 mg of prednisolone per day for ≥ 4 weeks
			MTX	19.7 (SD 7.6)[a]	5.2 (SD 1.1)	
			IFX and MTX	16.0 (SD 7.7)[a]	5.4 (SD 1.1)	

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; AMPLE, abatacept vs. adalimumab in biologic-naive RA patients with background MTX; AVERT, Assessing Very Early Rheumatoid arthritis Treatment; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; DMARD, disease-modifying antirheumatic drug; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; ITT, intention to treat; NR, not reported; Q1/Q2/Q3/Q4, quartile 1/quartile 2/quartile 3/quartile 4; s.c., subcutaneous; TEAR, Treatment of Early Aggressive Rheumatoid arthritis.

a Disease duration.
b From Bathon *et al.*[112]
c Calculated.
d Symptom duration.
e From Emery *et al.*[116]
f DAS28-CRP.
g From Moreland *et al.*[117]
h Median.
i From Choy *et al.*[114]
j From St Clair *et al.*[87]
k Median (range).

The duration of RA was reported in some studies as disease duration and in others as symptom duration. Disease duration ranged from a mean of 1.4 months[107] to a mean of 17.9 months,[101] and from a median of 1.0 month[109] to a median of 24.0 months.[110] Symptom duration ranged from a mean of 6.0 months to a mean of 7.1 months,[104] and from a median of 5.3 months to a median of 6.0 months.[103] Baseline DAS28, when reported, ranged from a mean of 5.3[101,104] to a mean of 6.7,[100] and one study reported DAS, with a baseline mean of 4.4,[103] indicating severe RA in all populations for which the DAS28 or the DAS at baseline was reported. Three studies did not report the DAS28 or the DAS at baseline.[102,107,108] Participants were DMARD naive in two studies[103,106] and MTX naive in three studies.[100,102,108] One study reported that participants were DMARD naive or treated with a maximum of one DMARD, which could be an antimalarial agent (30% of the sample) or auranofin (22% of the sample).[107] One study reported prior DMARD use in 14% of the sample,[109] one study reported that participants had to be bDMARD naive with an inadequate response to MTX[110] and one study reported that participants had to be receiving a stable dose of MTX.[101] One study reported that participants were bDMARD naive, with prior MTX use in 21% of the sample,[105] and one study reported that participants were MTX naive or had received a low dose of MTX previously for ≤ 4 weeks with a 1-month washout period.[104]

Results: synthesis of primary studies

Treatment prediction models presents the findings for clinical prediction models developed according to specific treatments. *Prediction of treatment effect by anticitrullinated protein/peptide anti-body status at baseline: erosions* presents information regarding patient and/or disease characteristics that are potential treatment effect modifiers.

Tables 16 and *17* provide the estimates of the within-treatment responses and interaction effects by baseline variable for continuous outcomes. *Appendix 10* presents plots of the estimates of the within-treatment responses by baseline variable. The results are presented by study because the combination of outcomes and predictors generated no studies that shared any treatment in common, so that a formal synthesis was not possible.

Treatment prediction models

Only one of the clinical prediction models involving multiple treatments that was reported in review 1 investigated the potential interactions between treatments and baseline variables.[79] Consequently, it was not possible to distinguish between covariates that were prognostic and those that were treatment effect modifiers in most clinical prediction models. Visser *et al.*[79] investigated the interaction between treatments and baseline variables and reported that there were no statistically significant interactions between covariates (ACPA status, RF status, CRP tertile, erosion score) and treatments (initial MTX monotherapy, initial MTX and prednisone combination therapy and initial MTX and IFX combination therapy), although this may be because the analysis lacked sufficient power to detect such effects as being statistically significant.

Prediction of treatment effect by anticitrullinated protein/peptide anti-body status at baseline: erosions

The results from Mustila *et al.*[106] suggest that the effect of triple therapy (MTX and SSZ and HCQ) versus sequential monotherapy on erosions at 1 (see *Appendix 10*, *Figure 10*) and 2 years (see *Appendix 10*, *Figure 11*) was similar in patients who were ACPA positive and ACPA negative at baseline (i.e. scenario 1). However, at 3 (see *Appendix 10*, *Figure 12*), 4 (see *Appendix 10*, *Figure 13*) and 5 years (see *Appendix 10*, *Figure 14*), the observed effect of treatment was less in patients who were ACPA positive than the effect of treatment in patients who were ACPA negative at baseline (i.e. scenario 2), although the results were not statistically significant.

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
Prediction of treatment response by ACPA status at baseline: erosions								
Mustila (2011)[106] FIN-RACo Larsen score (absolute value)	ACPA+	MTX and SSZ and HCQ	1 year	46	5.91 (3.8 to 8.2)[a]	NR	NR	NR
		Sequential cDMARDs		46	10.21 (6.98 to 13.46)[a]	NR	NR	NR
	ACPA–	MTX and SSZ and HCQ		23	3.57 (1.52 to 5.93)[a]	NR	NR	NR
		Sequential cDMARDs		14	7.81 (3.21 to 12.56)[a]	NR	NR	NR
	ACPA+	MTX and SSZ and HCQ	2 years	46	8.82 (6.54 to 11.52)[a]	NR	NR	NR
		Sequential cDMARDs		46	14.61 (11.12 to 18.07)[a]	NR	NR	NR
	ACPA–	MTX and SSZ and HCQ		23	4.09 (1.82 to 6.44)[a]	NR	NR	NR
		Sequential cDMARDs		14	10.87 (5.83 to 16.22)[a]	NR	NR	NR
	ACPA+	MTX and SSZ and HCQ	3 years	46	12.57 (8.88 to 16.38)[a]	NR	NR	NR
		Sequential cDMARDs		46	18.52 (14.84 to 22.52)[a]	NR	NR	NR
	ACPA–	MTX and SSZ and HCQ		23	4.96 (2.26 to 7.86)[a]	NR	NR	NR
		Sequential cDMARDs		14	16.61 (8.99 to 24.34)[a]	NR	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	ACPA+	MTX and SSZ and HCQ	4 years	46	14.56 (11.21 to 18.15)[a]	NR	NR	NR
		Sequential cDMARDs		46	22.15 (18.01 to 26.48)[a]	NR	NR	NR
	ACPA–	MTX and SSZ and HCQ		23	5.77 (2.9 to 9.1)[a]	NR	NR	NR
		Sequential cDMARDs		14	20.31 (11.13 to 29.82)[a]	NR	NR	NR
	ACPA+	MTX and SSZ and HCQ	5 years	46	19.3 (13.69 to 25.26)[a]	NR	NR	NR
		Sequential cDMARDs		46	24.66 (20.22 to 29.33)[a]	NR	NR	NR
	ACPA–	MTX and SSZ and HCQ		23	7.62 (3.35 to 12.1)[a]	NR	NR	NR
		Sequential cDMARDs		14	21.06 (11.34 to 30.83)[a]	NR	NR	NR
Seegobin (2014)[109]	ACPA+	MTX and CsA and prednisolone	6 months	79	1.25 (0.28[b])	0.003	NR	NR
CARDERA		MTX		73	3.86 (0.8[b])		NR	NR
Change in Larsen score from baseline	ACPA–	MTX and CsA and prednisolone		28	0.48 (0.35[b])	0.093	NR	NR
		MTX		34	1.6 (0.55[b])	NR	NR	NR
	ACPA+	MTX and CsA and prednisolone	12 months	79	2.41 (0.52[b])	< 0.001	NR	NR
		MTX		73	6.92 (1.1[b])	NR	NR	NR
	ACPA–	MTX and CsA and prednisolone		28	1.36 (0.47[b])	0.409	NR	NR
		MTX		34	2.03 (0.66[b])	NR	NR	NR

continued

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	ACPA+	MTX and CsA and prednisolone	18 months	79	3.2 (0.66[b])	0.001	NR	NR
		MTX		73	8.52 (1.39[b])	NR	NR	NR
	ACPA–	MTX and CsA and prednisolone		28	1.66 (0.64[b])	0.388	NR	NR
		MTX		34	2.57 (0.79[b])	NR	NR	NR
	ACPA+	MTX and CsA and prednisolone	24 months	79	3.66 (0.7/2.27 to 5.05[c])	< 0.001	NR	NR
		MTX		73	9.58 (1.41/6.76 to 12.39[c])	NR	NR	NR
	ACPA–	MTX and CsA and prednisolone		28	1.7 (0.69/0.29 to 3.10[c])	0.335	NR	NR
		MTX		34	2.72 (0.77/1.15 to 4.29[c])	NR	NR	NR
	N/A	N/A	N/A	N/A	NR	NR	7.05[d]	< 0.001
Prediction of treatment response by ACPA status at baseline: disease activity								
Seegobin (2014)[109]	ACPA+	MTX and CsA and prednisolone	6 months	79	–1.98 (0.18[b])	< 0.001	NR	NR
CARDERA		MTX		73	–0.99 (0.17[b])	NR	NR	NR
Change in DAS28 from baseline	ACPA–	MTX and CsA and prednisolone		28	–1.43 (0.33[b])	0.792	NR	NR
		MTX		34	–1.32 (0.22[b])	NR	NR	NR
	ACPA+	MTX and CsA and prednisolone	12 months	79	–1.48 (0.18[b])	0.190	NR	NR
		MTX		73	–1.14 (0.19[b])	NR	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	ACPA–	MTX and CsA and prednisolone		28	–0.73 (0.33[b])	0.186	NR	NR
		MTX		34	–1.36 (0.33[b])	NR	NR	NR
	ACPA+	MTX and CsA and prednisolone	18 months	79	–1.64 (0.2[b])	0.356	NR	NR
		MTX		73	–1.37 (0.2[b])	NR	NR	NR
	ACPA–	MTX and CsA and prednisolone		28	–1.27 (0.37[b])	0.462	NR	NR
		MTX		34	–1.62 (0.3[b])	NR	NR	NR
	ACPA+	MTX and CsA and prednisolone	24 months	79	–1.84 (0.19[b])	0.087	NR	NR
		MTX		73	–1.36 (0.22[b])	NR	NR	NR
	ACPA–	MTX and CsA and prednisolone		28	–1.27 (0.32[b])	0.464	NR	NR
		MTX		34	–1.59 (0.3[b])	NR	NR	NR
	N/A	N/A	N/A	N/A	N/A	N/A	3.99[d]	0.008
Sokolove (2015)[110] AMPLE Mean change from baseline in DAS28-CRP	Anti-CCP2–	MTX and ABT (s.c. administration)	6 months	66	–1.9 (–1.76 to –2.2)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		54	–1.525 (–1.375 to –1.7)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q1 28–235 AU/ml	MTX and ABT (s.c. administration)		42	–2.05 (–1.8 to –2.23)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.425 (unreadable)[a,b,e]	NR	NR	NR

continued

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	Anti CCP2+; Q2 236–609 AU/ml	MTX and ABT (s.c. administration)		51	–2.1 (–1.9 to –2.3)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		46	–2.3 [–2.1 to (unreadable)][a,b,e]	NR	NR	NR
	Anti CCP2+; Q3 613–1046 AU/ml	MTX and ABT (s.c. administration)		46	–2.2 (–2.0 to –2.35)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.125 (–1.95 to –2.3)[a,b,e]	NR	NR	NR
	Anti CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration)		46	–2.6 (–2.4 to –2.8)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.5 (–2.3 to –2.675)[a,b,e]	NR	NR	NR
	Anti-CCP2–	MTX and ABT (s.c. administration)	1 year	66	–1.9 [–1.75 to (unreadable)][a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		54	–1.65 (–1.49 to –1.85)[a,b,e]	NR	NR	NR
	Anti CCP2+; Q1 28–235 AU/ml	MTX and ABT (s.c. administration)		42	–2.075 [–1.85 to (unreadable)][a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.275 (–2.075 to –2.48)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q2 236–609 AU/ml	MTX and ABT (s.c. administration)		51	–2.45 (–2.225 to –2.625)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		46	–2.38 (–2.15 to –2.58)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q3 613–104 AU/ml	MTX and ABT (s.c. administration)		46	–2.3 (–2.15 to –2.5)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.43 (–2.25 to –2.5)[a,b,e]	NR	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration)		46	–2.825 (–2.625 to –3.0)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.6 (–2.3 to –2.78)[a,e]	NR	NR	NR
	Anti-CCP2–	MTX and ABT (s.c. administration)	2 years	66	–1.7 (–1.56 to –1.9)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		54	–1.625 (–1.4 to –1.85)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q1 28–235 AU/ml	MTX and ABT (s.c. administration)		42	–2.2 [–1.925 to (unreadable)][a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.38 (–2.125 to –2.6)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q2 236–609 AU/ml	MTX and ABT (s.c. administration)		51	–2.55 (–2.28 to –2.7)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		46	–2.65 (–2. 35 to –2.83)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q3 613–1046 AU/ml	MTX and ABT (s.c. administration)		46	–2.5 (–2.25 to –2.7)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.5 (–2.275 to –2.675)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration)		46	–3.195 (–2.975 to –3.35)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–2.75 (–2.6 to –2.83)[a,b,e]	NR	NR	NR

continued

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
Prediction of treatment response by ACPA status at baseline: physical function (as assessed via the HAQ score)								
Seegobin (2014)[109]	N/A	N/A	N/A	N/A	N/A	N/A	0.48[d]	0.696
CARDERA								
Change in HAQ score from baseline								
Sokolove (2015)[110]	Anti-CCP2–	MTX and ABT (s.c. administration)	6 months	66	–0.48 (–0.4 to –0.54)[a,b,e]	NR	NR	NR
AMPLE		MTX and ADA (s.c. administration)		54	–0.25 (–0.18 to –0.32)[a,b,e]	NR	NR	NR
Mean change from baseline in HAQ-DI score	Anti-CCP2+; Q1 28–235 AU/ml	MTX and ABT (s.c. administration)		42	–0.49 (–0.42 to –0.575)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.63 (–0.55 to –0.71)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q2 236–609 AU/ml	MTX and ABT (s.c. administration)		51	–0.7 (–0.62 to –0.78)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		46	–0.58 (–0.49 to –0.67)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q3 613–1046 AU/ml	MTX and ABT (s.c. administration)		46	–0.72 (–0.63 to –0.815)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.59 (–0.50 to –0.67)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration)		46	–0.83 (–0.73 to –0.93)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.75 (–0.66 to –0.84)[a,b,e]	NR	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	Anti-CCP2–	MTX and ABT (s.c. administration)	1 year	66	–0.45 (–0.385 to –0.52)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		54	–0.3 (–0.23 to –0.37)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q1 28–235 AU/ml	MTX and ABT (s.c. administration)		42	–0.575 (–0.48 to –0.68)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.68 (–0.59 to –0.77)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q2 236–609 AU/ml	MTX and ABT (s.c. administration)		51	–0.69 (–0.62 to –0.77)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		46	–0.59 (–0.50 to –0.68)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q3 613–1046 AU/ml	MTX and ABT (s.c. administration)		46	–0.63 (–0.53 to –0.73)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.65 (–0.55 to –0.75)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration)		46	–0.93 (–0.83 to –1.035)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.72 (–0.63 to –0.81)[a,b,e]	NR	NR	NR
	Anti-CCP2–	MTX and ABT (s.c. administration)	2 years	66	–0.45 (–0.39 to –0.515)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		54	–0.32 (–0.25 to –0.38)[a,b,e]	NR	NR	NR

continued

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	Anti-CCP2+; Q1 28–235 AU/ml	MTX and ABT (s.c. administration)		42	–0.575 (–0.485 to –0.67)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.68 (–0.59 to –0.77)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q2 236–609 AU/ml	MTX and ABT (s.c. administration)		51	–0.66 (–0.57 to –0.75)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		46	–0.67 (–0.57 to –0.77)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q3 613–1046 AU/ml	MTX and ABT (s.c. administration)	2 years	46	–0.58 (–0.50 to –0.70)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.64 (–0.54 to –0.74)[a,b,e]	NR	NR	NR
	Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration)		46	–0.99 (–0.89 to –1.08)[a,b,e]	NR	NR	NR
		MTX and ADA (s.c. administration)		51	–0.81 (–0.71 to –0.90)[a,b,e]	NR	NR	NR
Prediction of treatment response by smoking status at baseline: disease activity								
Maska (2012)[105]	Non-smokers	MTX and ETN IT	1–2 years (mean)	NR	3.01 (1.3[f])	NR	NR	NR
TEAR		MTX and SSZ and HCQ IT		NR	3.24 (1.3[f])	NR	NR	NR
		MTX and ETN SUT		NR	3.31 (1.3[f])	NR	NR	NR
Mean DAS28 (absolute value)		MTX and SSZ and HCQ SUT		NR	3.07 (1.4[f])	NR	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
	Current smokers	MTX and ETN IT		NR	3.07 (1.2[f])	NR	NR	NR
		MTX and SSZ and HCQ IT		NR	3.15 (1.9[f])	NR	NR	NR
		MTX and ETN SUT		NR	3.2 (1.4[f])	NR	NR	NR
		MTX and SSZ and HCQ SUT		NR	3.2 (1.1[f])	NR	NR	NR
	Non-smokers	ETN and MTX (COM)	24 weeks	NR	3.89	NR	NR	NR
		MTX and SSZ and HCQ (COM)		NR	4.01	NR	NR	NR
	Current smokers	ETN and MTX (COM)		NR	3.81	NR	NR	NR
		MTX and SSZ and HCQ (COM)		NR	3.66	NR	NR	NR
	Non-smokers	ETN and MTX (COM)	48 weeks	NR	3.3	NR	NR	NR
		MTX and SSZ and HCQ (COM)		NR	3.33	NR	NR	NR
	Current smokers	ETN and MTX (COM)		NR	3.17	NR	NR	NR
		MTX and SSZ and HCQ (COM)		NR	3.33	NR	NR	NR
	Non-smokers	ETN and MTX (COM)	102 weeks	NR	2.93	NR	NR	NR
		MTX and SSZ and HCQ (COM)		NR	3.15	NR	NR	NR
	Current smokers	ETN and MTX (COM)		NR	2.93	NR	NR	NR
		MTX and SSZ and HCQ (COM)		NR	3.15	NR	NR	NR

continued

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
Prediction of treatment response by erosions at baseline: radiographic progression								
Pasero (1996)[107] Change from baseline in the Larsen–Dale EJC	Erosions at baseline	CsA	12 months	104	1.61 (0.35)[a]	NR	NR	NR
		Other cDMARDs		89	2.94 (0.30)[a]	NR	NR	NR
	No erosions at baseline	CsA		37	0.46 (0.18)[a]	NR	NR	NR
		Other cDMARDs		54	1.62 (0.32)[a]	NR	NR	NR
Pasero (1996)[107] Change from baseline in the Larsen–Dale damage score	Erosions at baseline	CsA		104	4.75 (0.89)[a]	NR	NR	NR
		Other cDMARDs		89	7.96 (0.93)[a]	NR	NR	NR
	No erosions at baseline	CsA		37	0.48 (0.96)[a]	NR	NR	NR
		Other cDMARDs		54	5.14 (1.28)[a]	NR	NR	NR
Smolen (2006)[100] ASPIRE Change from baseline in the SHS	SHS of < 2.6	MTX	Week 54	100	1.87		NR	NR
		MTX and IFX		231	0.83	< 0.05[g]	NR	NR
	SHS of ≥ 2.6 to < 10.5	MTX		87	4.98		NR	NR
		MTX and IFX		246	0.84	< 0.001[g]	NR	NR
	SHS of ≥ 10.5	MTX		92	3.78		NR	NR
		MTX and IFX		238	–0.41	< 0.001[g]	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
Prediction of treatment response by RF status at baseline: radiographic progression								
Vastesaeger (2009)[78]	RF of < 80 U/ml	MTX	Week 54	82	Reference		NR	NR
ASPIRE		MTX and IFX		201	0.38 (0.13[b,h])[a,i]	0.0030[g]	NR	NR
Increase of ≥ 5/year in the total SHS score	RF of 80–200 U/ml	MTX		73	Reference		NR	NR
		MTX and IFX		783	0.38 (0.14[b,h])[a,i]	0.0048[g]	NR	NR
	RF of > 200 U/ml	MTX		128	Reference		NR	NR
		MTX and IFX		341	0.54 (0.11[b,h])[a,i]	< 0.0001[g]	NR	NR
Prediction of treatment response by CRP level at baseline: radiographic progression								
Smolen (2006)[100]	CRP level of < 0.6 mg/dl	MTX	Week 54	93	1.7[a]		NR	NR
ASPIRE		MTX and IFX		232	1.15[a]	NS	NR	NR
Change from baseline in the SHS	CRP level of ≥ 0.6 to < 3 mg/dl	MTX		103	4.36[a]		NR	NR
		MTX and IFX		242	0.84[a]	< 0.001[g]	NR	NR
	CRP level of ≥ 3 mg/dl	MTX		86	5.99[a]		NR	NR
		MTX and IFX		248	1.35[a]	< 0.001[g]	NR	NR
Vastesaeger 2009[78]	CRP level of < 0.6 mg/dl	MTX		93	Reference		NR	NR
ASPIRE		MTX and IFX		232	0.15 (0.08[b,h])[a,i]	0.2172[g]	NR	NR
Increase of ≥ 5/year total SHS score	CRP level of 0.6–3.0 mg/dl	MTX		105	Reference		NR	NR
		MTX and IFX		252	0.51 (0.26[b,h])[a,i]	< 0.0001[g]	NR	NR
	CRP level of > 3.0 mg/dl	MTX		84	Reference		NR	NR
		MTX and IFX		238	0.65 (0.33[b,h])[a,i]	< 0.0001[g]	NR	NR

continued

TABLE 16 Within-treatment responses by outcome and baseline variable – continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
Prediction of treatment response by ESR at baseline: radiographic progression								
Smolen (2006)[100]	ESR of < 28 mm/hour	MTX	Week 54	93	2.88[a]		NR	NR
ASPIRE		MTX and IFX		223	(Unreadable)	< 0.05[g]	NR	NR
Change from baseline in the SHS	ESR of ≥ 28 to < 52 mm/hour	MTX		89	2.65[a]		NR	NR
		MTX and IFX		233	0.47[a]	< 0.001[g]	NR	NR
	ESR of ≥ 52 mm/hour	MTX		87	6.13[a]		NR	NR
		MTX and IFX		234	1.64[a]	< 0.001[g]	NR	NR
Vastesaeger (2009)[78]	ESR of < 21 mm/hour	MTX		57	Reference		NR	NR
ASPIRE		MTX and IFX		141	0.13 (0.16[b,h])[a,i]	0.3755[g]	NR	NR
Increase of ≥ 5/year in the total SHS score	ESR of 21–50 mm/hour	MTX		125	Reference		NR	NR
		MTX and IFX		313	0.45 (0.12[b,h])[a,i]	< 0.0001[g]	NR	NR
	ESR of > 50 mm/hour	MTX		87	Reference		NR	NR
		MTX and IFX		236	0.60 (0.12[b,h])[a,i]	< 0.0001[g]	NR	NR

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	Mean (SD/standard error/95% CI)	*p*-value for difference between treatment arms	Treatment effect statistic (SD/standard error/95% CI)	*p*-value for treatment effect
Prediction of treatment response by SJC at baseline: radiographic progression								
Vastesaeger (2009)[78]	SJC28 of < 10	MTX	Week 54	50	Reference		NR	NR
ASPIRE		MTX and IFX		145	0.31 (0.17[b,h])[a,i]	0.0524[g]	NR	NR
Increase of ≥ 5/year in the total SHS score	SJC28 of 10–17	MTX		146	Reference		NR	NR
		MTX and IFX		367	0.44 (0.10[b,h])[a,i]	< 0.0001[g]	NR	NR
	SJC28 of > 17	MTX		85	Reference		NR	NR
		MTX and IFX		210	0.51 (0.13[b,h])[a,i]	< 0.0001[g]	NR	NR

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; ADA, adalimumab; AMPLE, abatacept vs. adalimumab in biologic-naive RA patients with background MTX; anti-CCP2–, anticyclic citrullinated peptide-2 negative; anti-CCP2+, anticyclic citrullinated peptide-2 positive; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; COM, combination; EJC, eroded joint count; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; HAQ-DI, Health Assessment Questionnaire – disability index; IT, immediate therapy; N/A, not applicable; NR, not reported; NS, not significant; Q1/Q2/Q3/Q4, quartile 1/quartile 2/quartile 3/quartile 4; s.c., subcutaneous; SJC28, 28 swollen joint count; SUT, step-up therapy; TEAR, Treatment of Early Aggressive Rheumatoid arthritis.

a Extracted from graphical data.
b Standard error.
c Standard error/95% CI.
d Analysis of variance *F*-statistic (ACPA × treatment interaction).
e Adjusted mean changes from baseline were determined by analysis of covariance, with treatment and DAS28 (CRP) stratification as factors and baseline values as a covariate.
f Unclear whether or not this is a SD or a standard error.
g Vs. MTX.
h Calculated.
i Difference between treatment groups in the mean van der Waerden normal scores of the change of ≥ 5/year in total SHS.

TABLE 17 Interaction effects by outcome and baseline variable: continuous outcomes

First author (year), name of trial or cohort (if relevant)	Outcome	Variable	Treatment	Follow-up time point	Treatment effect	Interaction effect, mean (95% CI)	Figure	Scenario/summary
Prediction of treatment response by ACPA status at baseline: erosions								
Mustila (2011)[106] FIN-RACo	Erosions Larsen score (absolute value)	ACPA+/ACPA–	MTX and SSZ and HCQ vs. sequential cDMARDs	1 year	ACPA+: –4.30 ACPA–: –4.24	–0.06 (–6.68 to 6.56)	11	1
				2 years	ACPA+: –5.79 ACPA–: –6.78	0.99 (–6.32 to 8.30)	12	1
				3 years	ACPA+: –5.95 ACPA–: –11.65	5.70 (–4.23 to 15.63)	13	2[a]
				4 years	ACPA+: –7.59 ACPA–: –14.54	6.95 (–4.59 to 18.49)	14	2
				5 years	ACPA+: –5.36 ACPA–: –13.44	8.08 (–5.07 to 21.23)	15	2
Seegobin (2014)[109] CARDERA	Erosions Change in the Larsen score from baseline	ACPA+/ACPA–	MTX and CsA and prednisolone vs. MTX	6 months	ACPA+: –2.61 ACPA–: –1.12	–1.49 (–3.59 to 0.61)	16	2[b]
				12 months	ACPA+: –4.51 ACPA–: –0.67	–3.84 (–17.53 to 9.85)	17	2
				18 months	ACPA+: –5.32 ACPA–: –0.91	–4.41 (–8.02 to –0.80)	18	2, interaction effect statistically significant
				24 months	ACPA+: –5.92 ACPA–: –1.02	–4.90 (–8.59 to –1.21)	19	2, interaction effect statistically significant
Prediction of treatment response by ACPA status at baseline: disease activity								
Seegobin (2014)[109] CARDERA	Disease activity Change in the DAS28 from baseline	ACPA+/ACPA–	MTX and CsA and prednisolone vs. MTX	6 months	ACPA+: –0.99 ACPA–: –0.11	–0.88 (–1.80 to 0.04)	24	
				12 months	ACPA+: –0.34 ACPA–: 0.63	–0.97 (–2.02 to 0.08)	25	Qualitative interaction, not statistically significant
				18 months	ACPA+: –0.27 ACPA–: 0.35	–0.62 (–1.71 to 0.47)	26	Qualitative interaction, not statistically significant

First author (year), name of trial or cohort (if relevant)	Outcome	Variable	Treatment	Follow-up time point	Treatment effect	Interaction effect, mean (95% CI)	Figure	Scenario/summary
				24 months	ACPA+: –0.48 ACPA–: 0.32	–0.80 (–1.83 to 0.23)	27	Qualitative interaction, not statistically significant
Sokolove (2015)[110] AMPLE	Mean change from baseline in DAS28-CRP	Anti-CCP2– Anti-CCP2+; Q1 28–235 AU/ml Anti CCP2+; Q2 236–609 AU/ml Anti-CCP2+; Q3 613–1046 AU/ml Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration) vs. MTX and ADA (s.c. administration)	6 months	Anti-CCP2–: –0.38 Anti-CCP2+; Q1: 0.38 Anti-CCP2+; Q2: 0.20 Anti-CCP2+; Q3: –0.08 Anti-CCP2+; Q4: –0.10	Interaction with anti-CCP2–: Anti-CCP2+, Q1: 0.75 (Not estimable) Anti-CCP2+, Q2: 0.58 (–0.11 to 1.26) Anti-CCP2+, Q3: 0.30 (–0.36 to 0.96) Anti-CCP2+, Q4: 0.28 (–0.41 to 0.96)	32	No evidence of TE or interaction
				1 year	Anti-CCP2–: –0.25 Anti-CCP2+ Q1: 0.20 Anti-CCP2+ Q2: –0.07 Anti-CCP2+ Q3: 0.13 Anti-CCP2+ Q4: –0.23	Interaction with anti-CCP2–: Anti-CCP2+, Q1: 0.45 (–0.28 to 1.18) Anti-CCP2+, Q2: 0.18 (–0.58 to 0.94) Anti-CCP2+, Q3: 0.38 (–0.25 to 1.01) Anti-CCP2+, Q4: 0.02 (–0.80 to 0.85)	33	
				2 years	Anti-CCP2–: –0.08 Anti-CCP2+, Q1: 0.18 Anti-CCP2+, Q2: 0.10 Anti-CCP2+, Q3: 0.00 Anti-CCP2+, Q4: –0.45	Interaction with anti-CCP2–: Anti-CCP2+, Q1: 0.26 (–0.65 to 1.16) Anti-CCP2+, Q2: 0.18 (–0.77 to 1.12) Anti-CCP2+, Q3: 0.08 (–0.76 to 0.91) Anti-CCP2+ Q4: –0.37 (–1.11 to 0.37)	34	

continued

TABLE 17 Interaction effects by outcome and baseline variable: continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant)	Outcome	Variable	Treatment	Follow-up time point	Treatment effect	Interaction effect, mean (95% CI)	Figure	Scenario/summary
Prediction of treatment response by ACPA status at baseline – physical function (as assessed via the HAQ score)								
Seegobin (2014)[109] CARDERA	Change in the HAQ score from baseline	N/A	N/A	N/A			N/A	N/A
Sokolove (2015)[110] AMPLE	Physical function: mean change from baseline in the HAQ-DI score	Anti-CCP2– Anti-CCP2+; Q1 28–235 AU/ml Anti-CCP2+; Q2 236–609 AU/ml/ml Anti-CCP2+; Q4 1060–4894 AU/ml	MTX and ABT (s.c. administration) vs. MTX and ADA (s.c. administration)	6 months	Anti-CCP2–: –0.23 Anti-CCP2+, Q1: 0.14 Anti-CCP2+, Q2: –0.12 Anti-CCP2+, Q3: –0.13 Anti-CCP2+, Q4: –0.08	Interaction with anti-CCP2–: Anti-CCP2+, Q1: 0.37 (0.08 to 0.66) Anti-CCP2+, Q2: 0.11 (–0.20 to 0.42) Anti-CCP2+, Q3: 0.10 (–0.20 to 0.42) Anti-CCP2+, Q4: 0.15 (–0.19 to 0.49)	35	No evidence of TE or interaction
				1 year	Anti-CCP2–: –0.15 Anti-CCP2+, Q1: 1.26 Anti-CCP2+, Q2: –0.10 Anti-CCP2+, Q3: 0.02 Anti-CCP2+, Q4: –0.21	Interaction with anti-CCP2–: Anti-CCP2+, Q1: 1.41 (1.09 to 1.72) Anti-CCP2+, Q2: 0.05 (–0.24 to 0.34) Anti-CCP2+, Q3: 0.17 (–0.16 to 0.50) Anti-CCP2+, Q4: –0.06 (–0.38 to 0.26)	36	No evidence of TE or interaction

First author (year), name of trial or cohort (if relevant)	Outcome	Variable	Treatment	Follow-up time point	Treatment effect	Interaction effect, mean (95% CI)	Figure	Scenario/summary
				2 years	Anti-CCP2–: –0.13 Anti-CCP2+, Q1: 0.11 Anti-CCP2+, Q2: 0.01 Anti-CCP2+, Q3: 0.06 Anti-CCP2+, Q4: –0.18	Interaction with anti-CCP2–: Anti-CCP2+, Q1: 0.24 (–0.07 to 0.54) Anti-CCP2+, Q2: 0.14 (–0.15 to 0.43) Anti-CCP2+, Q3: 0.19 (–0.12 to 0.50) Anti-CCP2+, Q4: –0.05 (–0.38 to 0.28)	37	No evidence of TE or interaction
Prediction of treatment response by smoking status at baseline: disease activity								
Maska (2012)[105] TEAR	Disease activity Mean DAS28 (absolute value)	Non-smokers Current smokers	MTX and ETN IT vs. MTX and SSZ and HCQ IT vs. MTX and ETN SU vs. MTX and SSZ and HCQ SU	1–2 years (mean)			38	Cannot assess statistical significance
			ETN and MTX (COM) vs. MTX and SSZ and HCQ (COM)	24 weeks			39	Cannot assess statistical significance. Qualitative interaction
				48 weeks			40	3
				102 weeks			41	Not prognostic for either treatment
Prediction of treatment response by erosions at baseline: radiographic progression								
Pasero (1996)[107]	Radiographic progression Change from baseline in the Larsen–Dale EJC	Erosions at baseline: yes/no	CsA vs. other cDMARDs	12 months	Erosions at baseline: –1.33 No erosions at baseline: –1.16	–0.17 (–1.33 to 0.99)	42	1, prognostic of response but not a treatment effect modifier
Pasero (1996)[107]	Change from baseline in the Larsen–Dale damage score	Erosions at baseline: yes/no	CsA vs. other cDMARDs	12 months	Erosions at baseline: –3.21 No erosions at baseline: –4.66	1.45 (–2.57 to 5.47)	43	1
Smolen (2006)[100] ASPIRE	Radiographic progression Change from baseline in the SHS	SHS of < 2.6 SHS of ≥ 2.6 to < 10.5 SHS of ≥ 10.5	MTX vs. IFX	Week 54			44	Could not formally assess interaction. Suggest a treatment effect modifier

continued

TABLE 17 Interaction effects by outcome and baseline variable: continuous outcomes (*continued*)

First author (year), name of trial or cohort (if relevant)	Outcome	Variable	Treatment	Follow-up time point	Treatment effect	Interaction effect, mean (95% CI)	Figure	Scenario/summary
Prediction of treatment response by RF status at baseline – radiographic progression								
Vastesaeger (2009)[78] ASPIRE	Erosions/radiographic progression Increase of ≥ 5/year in the total SHS score	RF of < 80 U/ml RF of 80–200 U/ml RF of > 200 U/ml	MTX vs. MTX and IFX	Week 54	RF of < 80 U/ml: 0.38 RF of 80–200 U/ml: 0.38 RF of > 200 U/ml: 0.54	RF of 80–200 U/ml and RF of < 80 U/ml: 0.00 (–0.38 to 0.38) RF of > 200 U/ml and RF of < 80 U/ml: 0.16 (–0.17 to 0.49)		
Prediction of treatment response by CRP at baseline: radiographic progression								
Smolen (2006)[100] ASPIRE Change in SHS from baseline	Radiographic progression Change in SHS from baseline	CRP level of < 0.6 mg/dl CRP level of ≥ 0.6 to < 3 mg/dl CRP level of ≥ 3 mg/dl	MTX vs. MTX and IFX	Week 54			45	3, could not formally assess interaction
Vastesaeger (2009)[78] ASPIRE	Increase of ≥ 5/year in the total SHS score	CRP level of < 0.6 mg/dl CRP level of 0.6–3.0 mg/dl CRP level of > 3.0 mg/dl	MTX vs. MTX and IFX	Week 54	CRP level of < 0.6 mg/dl: 0.15 CRP level of 0.6–3.0 mg/dl: 0.51 CRP level of > 3.0 mg/dl: 0.65	CRP level of 0.6–3.0 mg/dl and CRP level of < 0.6 mg/dl: 0.36 (0.02 to 0.70) CRP level of > 3.0 mg/dl and CRP level of < 0.6 mg/dl: 0.50 (0.15 to 0.85)		

First author (year), name of trial or cohort (if relevant)	Outcome	Variable	Treatment	Follow-up time point	Treatment effect	Interaction effect, mean (95% CI)	Figure	Scenario/summary
Prediction of treatment response by ESR at baseline: radiographic progression								
Smolen (2006)[100] ASPIRE	Change in SHS from baseline	ESR of < 28 mm/hour ESR of ≥ 28 to < 52 mm/hour ESR of ≥ 52 mm/hour	MTX vs. MTX and IFX	Week 54			46	Could not formally assess interaction. Suggest a treatment effect modifier
Vastesaeger (2009)[78] ASPIRE	Increase of ≥ 5/year in the total SHS score	ESR of < 21 mm/hour ESR of 21–50 mm/hour ESR of > 50 mm/hour	MTX vs. MTX and IFX	Week 54	ESR of < 21 mm/hour: 0.13 ESR of 21–50 mm/hour: 0.45 ESR of > 50 mm/hour: 0.60	ESR of 21–50 mm/hour and an ESR of < 21 mm/hour: 0.32 (–0.07 to 0.71) ESR of > 50 mm/hour and an ESR of < 21 mm/hour: 0.47 (0.07 to 0.87)		
Prediction of treatment response by SJC at baseline: radiographic progression								
Vastesaeger (2009)[78] ASPIRE	Increase of ≥ 5/year in the total SHS score	SJC28 of < 10 SJC28 of 10–17 SJC28 of > 17	MTX vs. MTX and IFX	Week 54	SJC28 of < 10: 0.31 SJC28 10–17: 0.44 SJC28 of > 17: 0.51	SJC28 of 10–17 and SJC28 of < 10: 0.13 (–0.26 to 0.52) SJC28 of > 17 and SJC28 of < 10: 0.20 (–0.22 to 0.62)		

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; AMPLE, abatacept vs. adalimumab in biologic-naive RA patients with background MTX; anti-CCP2–, anticyclic citrullinated peptide-2 negative; anti-CCP2+, anticyclic citrullinated peptide-2 positive; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; COM, combination; EJC, eroded joint count; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; HAQ-DI, Health Assessment Questionnaire – disability index; IT, immediate therapy; N/A, not applicable; Q1/Q2/Q3/Q4, quartile 1/quartile 2/quartile 3/quartile 4; s.c., subcutaneous; SJC28, 28 swollen joint count; SU, step-up; TEAR, Treatment of Early Aggresive Rheumatoid arthritis.

a Treatment effect favoured ACPA-negative patients, but was not statistically significant.

b Treatment effect favours ACPA-positive patients, but was not statistically significant.

Results from Seegobin *et al.*[109] (see *Appendix 10*, *Figures 15–18*) suggest that the effect of triple therapy (MTX and CsA and prednisolone) versus MTX on erosions was greater in patients who were ACPA positive than the effect of treatment in patients who were ACPA negative at baseline (scenario 2). At 18 (see *Appendix 10*, *Figure 17*) and 24 months (see *Appendix 10*, *Figure 18*), the interaction effect was statistically significant (–4.41, 95% CI –8.02 to –0.80; –4.9, 95% CI –8.59 to –1.21, respectively).

Seegobin *et al.*[109] performed a repeated-measures analysis of variance (ANOVA) examining the interaction between treatment and ACPA status at baseline on the change from baseline in Larsen score, and reported a significant treatment × ACPA interaction ($F = 7.05$; $p < 0.001$) when treatment was one of the four randomised treatment arms (CsA, prednisolone, MTX monotherapy or MTX and CsA and prednisolone triple therapy).

Prediction of treatment effect by anticitrullinated protein/peptide anti-body status at baseline: disease activity

The results from Seegobin *et al.*[109] (see *Appendix 10*, *Figures 23–26*) suggest that there was a qualitative interaction between treatment and ACPA status at baseline and at 12, 18 and 24 months; patients who were ACPA negative at baseline had a worse change from the baseline DAS28 when treated with triple therapy (MTX and CsA and prednisolone) than the effect of being treated with MTX, whereas patients had a better change from baseline in DAS28 when treated with triple therapy (MTX and CsA and prednisolone) than the effect of being treated with MTX. However, these effects were not statistically significant.

Seegobin *et al.*[109] performed a repeated measures ANOVA examining the interaction between treatment and ACPA status at baseline on the change from the baseline DAS28, and reported a significant treatment × ACPA interaction ($F = 3.99$; $p = 0.008$) when treatment was one of the four randomised treatment arms [(1) CsA, (2) prednisolone, (3) MTX monotherapy or (4) MTX and CsA and prednisolone triple therapy].

Sokolove *et al.*[110] examined the effect of treatment [MTX and ABT (subcutaneous administration) vs. MTX and ADA (subcutaneous administration)] by anti-CCP2 status (negativity and four quartiles of anti-CCP2 positivity) on the change from baseline in DAS28-CRP at multiple time points up to 2 years (this study examined changes at 6 months, 1 year and 2 years for consistency with other evidence, because it was not feasible to examine all time points). There was no evidence of a difference in the effect of treatments or that the treatment effect varied according to anti-CCP2 status at baseline and at 6 months, and at 1 and 2 years (see *Appendix 10*, *Figures 31–33*).

Prediction of treatment effect by anticitrullinated protein/peptide anti-body status at baseline: physical function

Seegobin *et al.*[109] performed a repeated measures ANOVA examining the interaction between treatment and ACPA status at baseline on the change from the baseline HAQ score, but this was not statistically significant ($F = 0.48$; $p = 0.696$) when treatment was one of the four randomised treatment arms [(1) CsA, (2) prednisolone, (3) MTX monotherapy or (4) MTX and CsA and prednisolone triple therapy].

Sokolove *et al.*[110] examined the effect of treatment [MTX and ABT (subcutaneous administration) vs. MTX and ADA (subcutaneous administration)] by anti-CCP2 status (negativity and four quartiles of anti-CCP2 positivity) on the change from the baseline HAQ – disability index (HAQ-DI) score at multiple time points up to 2 years (we examined changes at 6 months, and at 1 and 2 years for consistency with other evidence, because it was not feasible to examine all time points). There was no evidence of a difference in the effect of treatments or that treatment effect varied according to anti-CCP2 status at baseline at 6 months and at 1 and 2 years (see *Appendix 10*, *Figures 34* and *35*).

Prediction of treatment effect by anticitrullinated protein/peptide anti-body status at baseline: remission

Results from Huizinga *et al.*[104] (*Tables 18* and *19*) suggest that the effect of ABT versus MTX on DAS28-CRP remission at 1 year was worse for patients who were ACPA positive at baseline than for those who were ACPA negative at baseline (ratio of ORs 0.57); however, this was not statistically significant (95% CI 0.19 to 1.69). The effect of ABT and MTX versus MTX on DAS28-CRP remission at 1 year was better in patients who were ACPA positive at baseline than in those who were ACPA negative at baseline (ratio of odds ratios 1.33), but this was not statistically significant (95% CI 0.45 to 3.90).

Prediction of treatment effect by smoking status at baseline: disease activity

It was not possible to formally assess the interaction effect between treatment and smoking status at baseline on DAS28 disease activity in the Maska *et al.*[105] study because standard errors were not available. The results of the comparison of ETN and MTX with MTX and SSZ and HCQ were inconsistent at 24, 48 and 102 weeks. At 24 weeks, there was a suggestion of a qualitative interaction between treatment and smoking status (see *Appendix 10*, *Figure 38*); patients who were non-smokers had a lower mean response when treated with ETN and MTX than those who were treated with MTX and SSZ and HCQ, whereas patients who were current smokers had a higher mean response when treated with ETN and MTX than those who were treated with MTX and SSZ and HCQ. At 48 weeks (see *Appendix 10*, *Figure 39*), the results suggested that smoking status was not prognostic in the case of ETN and MTX, whereas patients who were current smokers had a lower mean response when treated with ETN and MTX than non-smokers (i.e. scenario 3). At 102 weeks (see *Appendix 10*, *Figure 40*), the results suggested that smoking status was not a prognostic factor for both treatments.

Prediction of treatment effect by erosions at baseline: radiographic progression

The results from Pasero *et al.*[107] suggest that the presence of erosion versus the absence of erosion was prognostic of response but was not a treatment effect modifier for CsA versus other cDMARDs at 12 months with respect to the change from baseline in the Larsen–Dale eroded joint count (scenario 1; see *Appendix 10*, *Figure 41*) and with respect to the change from baseline in the Larsen–Dale damage score (scenario 1; see *Appendix 10*, *Figure 42*).

It was not possible to formally assess the interaction effect between treatment and SHS at baseline in the Smolen *et al.*[100] study, which reported baseline SHS in tertiles because standard errors were not available. The observed results suggest that SHS is a treatment effect modifier of the effect of MTX and IFX versus MTX on radiographic progression, but that SHS might not be prognostic for MTX and IFX (see *Appendix 10*, *Figure 43*).

Smolen *et al.*[100] reported a significant inverse correlation between erosions at baseline and change from baseline in SHS of > 0 at week 54 for the MTX and IFX treatment arm ($r = -0.19$; $p < 0.0001$), but not for the MTX arm ($r = 0.07$; $p = 0.25$; *Table 20*); this suggests that erosions may be a treatment effect modifier, but that it is not prognostic for MTX.

Smolen *et al.*[100] also performed separate within-treatment logistic regression analyses of worsening joint damage at week 54, adjusting for baseline characteristics on their continuous scales. The estimated ORs per unit change in covariate were generally small and were only statistically significant for the SHS for patients treated with MTX and IFX. In spite of this finding, the results suggest that the SHS may have little prognostic value in predicting the response for both MTX and IFX and MTX alone. When formally comparing the ORs between treatments, the results suggest that there were small differences in the effect of MTX and IFX versus MTX on worsening joint damage at week 54 by baseline SHS (ratio of ORs 0.98, 95% CI 0.96 to 1.00).

TABLE 18 Prediction of response to treatment: dichotomous outcomes

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	OR (SD/standard error/95% CI)	Number (%) of cases in category group
Prediction of treatment response by ACPA status at baseline: remission						
Huizinga (2015)[104]	Anti-CCP2 IgM positive	ABT (s.c. administration) and MTX	12 months	66	2.21[a]	43[b] (65.1%)
AVERT					Log-OR: 0.79 (variance: 0.12)	
DAS28-CRP level of < 2.6		ABT (s.c. administration)		62	0.70[a]	23[b] (37.4%)
					Log-OR: –0.36 (variance 0.13)	
		MTX		72	Reference	33[b] (45.6%)
	Anti-CCP2 IgM negative	ABT (s.c. administration) and MTX		52	1.67[a]	30[b] (57.8%)
					Log-OR: 0.51 (variance 0.18)	
		ABT (s.c. administration)		50	1.22[a]	25[b] (50.4%)
					Log-OR: 0.20 (variance 0.18)	
		MTX		40	Reference	18[b] (45.0%)
Prediction of treatment response by BMI at baseline: disease activity (DAS response)						
Heimans (2013)[103]	BMI of < 25 kg/m^2	MTX initial monotherapy	1 year	NR	Reference	NR
BeSt	BMI of ≥ 25 kg/m^2			NR	1.04 (0.82 to 1.31)[c,d]	NR
DAS of > 2.4					1.05 (0.84 to 1.30)[d,e]	
					Log-RR: 0.05 (standard error 0.11)[e]	
	BMI of < 25 kg/m^2	MTX and SSZ and tapered prednisone		NR	Reference	NR
	BMI of ≥ 25 kg/m^2			NR	1.37 (0.63 to 2.75)[c,d]	NR
					1.46 (0.75 to 2.83)[d,e]	
					Log-RR: 0.38 (standard error 0.34)[d]	

First author (year), name of trial or cohort (if relevant), measurement of outcome	Variable	Treatment	Follow-up time point	Sample size (*n*)	OR (SD/standard error/95% CI)	Number (%) of cases in category group
	BMI of < 25 kg/m^2	MTX and IFX		NR	Reference	NR
	BMI of ≥ 25 kg/m^2			NR	2.12 (0.93 to 4.83)[c,d]	NR
					2.20 (0.99 to 4.92)[d,e]	
					Log-RR: 0.79 (standard error 0.41)[e]	

ABT, abatacept; anti-CCP2, anticyclic citrullinated peptide-2; AVERT, Assessing Very Early Rheumatoid arthritis Treatment; IgM, immunoglobulin M; NR, not reported; RR, relative risk; s.c., subcutaneous.

a Vs. MTX.
b Calculated.
c Unadjusted relative risk (95% CI).
d Relative to a BMI of < 25 kg/m^2.
e Adjusted relative risk (95% CI) – adjusted for sex, age, smoking status, RF status and baseline DAS.

TABLE 19 Interaction effects by outcome and variable: dichotomous outcomes

First author (year), name of trial or cohort (if relevant)	Variable	Comparison	Follow-up time point	OR	Interaction effect, ratio of ORs (95% CI)
Prediction of treatment response by ACPA status at baseline: remission					
Huizinga (2015)[104]	ACPA status	ABT vs. MTX	1 year	ACPA+: 0.70	0.57 (95% CI 0.19 to 1.68)
DAS28-CRP remission				ACPA–: 1.22	
		ABT and MTX vs. MTX		ACPA+: 2.21	1.33 (95% CI 0.45 to 3.90)
				ACPA–: 1.67	
Prediction of treatment response by BMI at baseline: disease activity (DAS response)					
Heimans (2013)[103]	BMI	BMI of ≥ 25 kg/m^2 vs. BMI of < 25 kg/m^2	1 year	MTX and SSZ and tapered prednisone: 1.46[a]	1.39[b] (95% CI 0.43 to 2.79)
BeSt				MTX initial monotherapy: 1.05[a]	
DAS of > 2.4				MTX and IFX: 2.20[a]	2.10[b] (95% CI 0.91 to 4.82)
				MTX initial monotherapy: 1.05[a]	
Prediction of treatment response by erosions at baseline: radiographic progression					
Smolen (2006)[100]	SHS	N/A[c]	Week 54	MTX and IFX: 0.99[d]	0.98 (95% CI 0.96 to 1.00)
ASPIRE				MTX: 1.01[d]	
Worsening radiographic joint damage (change in the SHS of > 0)					
Prediction of treatment response by RF status at baseline: radiographic progression					
Smolen (2006)[100]	RF status	N/A[c]	Week 54	MTX and IFX: 1.00[d]	1.00 (95% CI 1.00 to 1.00)
ASPIRE				MTX: 1.00[d]	
Worsening radiographic joint damage (change in the SHS of > 0)					

First author (year), name of trial or cohort (if relevant)	Variable	Comparison	Follow-up time point	OR	Interaction effect, ratio of ORs (95% CI)
Prediction of treatment response by CRP level at baseline: radiographic progression					
Smolen (2006)[100]	CRP level	N/A[c]	Week 54	MTX and IFX: 1.03[d]	0.99 (95% CI 0.86 to 1.13)
ASPIRE				MTX: 1.05[d]	
Worsening radiographic joint damage (change in the SHS of > 0)					
Prediction of treatment response by ESR at baseline: radiographic progression					
Smolen (2006)[100]	ESR	N/A[c]	Week 54	MTX and IFX: 1.00[d]	0.99 (95% CI 0.97 to 1.00)
ASPIRE				MTX: 1.02[d]	
Worsening radiographic joint damage (change in the SHS of > 0)					
Prediction of treatment response by SJC at baseline: radiographic progression					
Smolen (2006)[100]	SJC	N/A[c]	Week 54	MTX and IFX: 1.00[d]	0.96 (95% CI 0.93 to 1.00)
ASPIRE				MTX: 1.04[d]	
Worsening radiographic joint damage (change in the SHS of > 0)					

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; AVERT, Assessing Very Early Rheumatoid arthritis Treatment; N/A, not applicable; s.c., subcutaneous.

a Relative risk.

b Ratio of relative risks.

c Within-treatment analysis.

d Within-treatment estimate of the change in the odds for a unit change in the predictor variable.

TABLE 20 Prediction of response to treatment: correlations

First author (year), name of trial or cohort (if relevant)	Treatment	Follow-up time point	Sample size (*n*)	Correlation coefficient	*p*-value for correlation coefficient	Regression coefficient	*p*-value for regression coefficient
Correlations between erosions at baseline and radiographic progression at follow-up							
Smolen (2006)[100]	MTX	Week 54	279	$r = 0.07$	0.2511	$\beta = 0.005$	0.583
ASPIRE	MTX and IFX		715	$r = -0.19$	< 0.0001	$\beta = -0.016$	0.007
Worsening radiographic joint damage (change in the SHS of > 0)							OR 0.99 (95% CI 0.97 to 1.0)
Correlations between RF status at baseline and radiographic progression at follow-up							
Smolen (2006)[100]	MTX	Week 54	282[a]	$r = 0.13$	0.0324	$\beta = -0.0003$	0.491
ASPIRE	MTX and IFX		722[a]	$r = 0.05$	0.1906	$\beta = 0.00$	0.695
Worsening radiographic joint damage (change in the SHS of > 0)							
Correlations between CRP level at baseline and radiographic progression at follow-up							
Garnero (2002)[102]	MTX	12 months	39	$r = 0.18$	NR (NS)	NR	NR
Change from baseline in the SHS erosion score	ETN		77	$r = 0.09$	NR (NS)	NR	NR
Garnero 2002[102]	MTX	12 months	39	$r = 0.28$	NR (NS)	NR	NR
Change from baseline in the SHS total score	ETN		77	$r = 0.18$	NR (NS)	NR	NR
Smolen (2006)[100]	MTX	Week 54	282	$r = 0.24$	< 0.0001	$\beta = 0.048$	0.43
ASPIRE	MTX and IFX		722	$r = 0.03$	0.4643	$\beta = 0.033$	0.291
Worsening radiographic joint damage (change in the SHS of > 0)							
Taylor (2004)[101]	MTX	54 weeks	12	$r = 0.58$	0.077	NR	NR
Change from baseline in the SHS	MTX and IFX		12	$r = -0.19$	0.562	NR	NR

First author (year), name of trial or cohort (if relevant)	Treatment	Follow-up time point	Sample size (*n*)	Correlation coefficient	*p*-value for correlation coefficient	Regression coefficient	*p*-value for regression coefficient
Correlations between ESR at baseline and radiographic progression at follow-up							
Smolen (2006)[100]	MTX	Week 54	269	$r = 0.27$	< 0.0001	$\beta = 0.018$	0.003
ASPIRE							OR 1.02 (95% CI 1.01 to 1.03)
Worsening radiographic joint damage (change in the SHS of > 0)	MTX and IFX		690	$r = 0.05$	0.2356	$\beta = 0.004$	0.335
Rau (1998)[108]	MTX	6 months	87	$r = 0.41$	< 0.001	NR	NR
Radiographic progression (change in the Rau-modified Larsen/Sharp score)	GSTM		87	$r = 0.24$	0.04	NR	NR
	MTX	12 months	87	$r = 0.41$	< 0.001	NR	NR
	GSTM		87	$r = 0.25$	< 0.03	NR	NR
Correlations between SJC at baseline and radiographic progression at follow-up							
Smolen (2006)[100]	MTX	Week 54	282[a]	$r = 0.16$	0.0088	$\beta = 0.039$	0.010
ASPIRE							OR 1.04 (95% CI 1.01 to 1.07)
Worsening radiographic joint damage (change in the SHS of > 0)	MTX and IFX		722[a]	$r = -0.01$	0.7291	$\beta = 0.002$	0.866
Correlations between vascularity of synovium using PDUS at baseline and radiographic progression at follow-up							
Taylor (2004)[101]	MTX	54 weeks	12	$r = 0.78$	0.005	NR	NR
Change from baseline in the SHS	MTX and IFX		12	$r = -0.28$	0.372	NR	NR

NR, not reported; NS, not significant.
a Number analysed in efficacy analyses.

Prediction of treatment effect by rheumatoid factor status at baseline: erosions/ radiographic progression

Smolen *et al.*[100] (see *Table 20*) reported a significant correlation between RF at baseline and change in the SHS of > 0 at week 54 for the MTX treatment arm ($r = 0.13$; $p = 0.03$), but not for the MTX and IFX arm ($r = 0.05$; $p = 0.19$). However, RF at baseline was not associated with a change in the SHS of > 0 from baseline to week 54 in separate logistic regression analyses by treatment group, adjusting for baseline demographic and other clinical characteristics (no further details reported) in the MTX and IFX arm ($\beta = 0.00$; $p = 0.70$) or the MTX arm ($\beta = -0.0003$; $p = 0.49$) (see *Table 20*).

Vastesaeger *et al.*[78] analysed the change from baseline in RRP (≥ 5/year in the total modified SHS score) using an ANOVA on the van der Waerden score, and presented the results of the effect of MTX and IFX versus MTX by RF subgroups. There was a suggestion of a treatment (i.e. MTX and IFX vs. MTX) by RF subgroup interaction, with patients who had > 200 U/ml of RF having a greater effect when treated with MTX and IFX versus MTX than patients with a lower RF score, although this was not statistically significant.

Rau *et al.*[108] performed separate multivariable within-treatment linear regression analyses for MTX and GSTM, including covariates for tender joint count, SJC, Activities of Daily Living (ADL) score, ESR, CRP level and RF status on radiographic change between months 0–6 and 0–12. Of these, the authors found only ESR to be statistically significant ($\beta = 0.49$, $p = 0.001$ for progression between 0 and 6 months; $\beta = 0.39$, $p = 0.007$ for progression between 0 and 12 months) for MTX. None of the covariates was statistically significant for GSTM. Thus, RF status was not found to be prognostic for MTX and GSTM (scenario 4).

Prediction of treatment effect by C-reactive protein level at baseline: radiographic progression

It was not possible to formally assess the interaction between treatment and CRP level at baseline in the Smolen *et al.*[100] study, which reported baseline CRP level in tertiles because standard errors were not available. The observed results suggest an increasing effect of MTX versus MTX, with higher levels of baseline CRP. The combination of MTX and IFX seems to have an effect on radiographic progression at all levels of CRP at baseline; this effect was not observed in the case of MTX. Baseline CRP level appears to be a treatment modifier with respect to MTX and IFX and MTX alone, but does not appear to be prognostic for MTX and IFX (scenario 3) (see *Appendix 10*, *Figure 44*).

Smolen *et al.*[100] reported a significant correlation between CRP level at baseline and change in the SHS of > 0 at week 54 for the MTX treatment arm ($r = 0.24$; $p < 0.0001$), but not for the MTX and IFX arm ($r = 0.03$; $p = 0.46$); this supports the assertion that MTX and IFX treatment has an effect irrespective of CRP level at baseline and that CRP level at baseline is a treatment effect modifier. However, CRP level at baseline was not associated with a change in the SHS of > 0 from baseline to week 54 in separate logistic regression analyses, adjusting for baseline demographic and other clinical characteristics (no further details reported) in the MTX and IFX arm ($\beta = 0.033$; $p = 0.29$) or the MTX arm ($\beta = 0.048$; $p = 0.43$) (see *Table 20*).

Vastesaeger *et al.*[78] analysed the change from baseline in RRP (≥ 5/year in the total modified SHS score) using an ANOVA on the van der Waerden score, and presented the results of the effect of MTX and IFX versus MTX by CRP subgroups. There was a suggestion of a treatment interaction (i.e. MTX and IFX vs. MTX) by CRP subgroup, with the effect of MTX and IFX being greater with higher baseline CRP levels, although the results were not statistically significant.

Garnero *et al.*[102] (see *Table 19*) reported no significant correlations between CRP level at baseline and change from baseline in the SHS erosion score in either the MTX or the ETN treatment arm at 12 months ($r = 0.18$ and $r = 0.09$, respectively; *p*-values not reported). Likewise, no significant associations were reported between CRP level at baseline and change from baseline in the SHS total score in either the MTX or ETN arm at 12 months ($r = 0.28$ and $r = 0.18$, respectively; *p*-values not reported). However, in both cases the observed association was greater for patients treated with MTX, which may indicate that CRP level at baseline is a treatment effect modifier with respect to the effect of MTX versus ETN.

Taylor *et al.*[101] (see *Table 19*) reported no significant associations between CRP level at baseline and change from baseline in the SHS score in either the MTX treatment arm or the MTX and IFX treatment arm at 54 weeks ($r = 0.58$, $p = 0.08$; and $r = -0.19$, $p = 0.56$, respectively). However, in both cases the observed association was greater for patients treated with MTX, which may indicate that CRP level at baseline is a treatment effect modifier with respect to the effect of MTX and IFX versus MTX.

Rau *et al.*[108] performed separate multivariable within-treatment linear regression analyses for MTX and GSTM, including covariates for tender joint count, SJC, ADL score, ESR, CRP level and RF status on radiographic change between months 0–6 and 0–12. Of these, the authors found only ESR to be statistically significant (data previously shown), with no predictive effect of CRP level for either treatment (data not shown) for MTX. None of the covariates was statistically significant for GSTM. Thus, CRP level was not found to be prognostic for MTX and GSTM (scenario 4).

Prediction of treatment effect by erythrocyte sedimentation rate at baseline: radiographic progression

It was not possible to formally assess the interaction between treatment and ESR at baseline in the Smolen *et al.*[100] study, which reported baseline ESR in tertiles, because standard errors were not available, and it was not possible to extract the mean from the published graph for patients treated with IFX and MTX and with a baseline ESR of < 28 mm/hour. Nevertheless, the observed results suggest that a baseline ESR of < 28 mm/hour and ≥ 28 to < 52 mm/hour may not be prognostic of response for MTX and IFX and MTX alone, but that it may be a treatment effect modifier for patients with a baseline ESR of ≥ 52 mm/hour (see *Appendix 10*, *Figure 45*).

Smolen *et al.*[100] (see *Table 20*) reported a significant correlation between ESR at baseline and the change from baseline in the SHS of > 0 for the MTX treatment arm ($r = 0.27$; $p < 0.0001$) but not for the MTX and IFX treatment arm ($r = 0.05$; $p = 0.24$); this supports the assertion that treatment with MTX and IFX has an effect irrespective of ESR at baseline and that ESR at baseline is a treatment effect modifier. ESR at baseline was found to be significantly associated with a change in the SHS of > 0 from baseline to week 54 in separate logistic regression analyses, adjusting for baseline demographic characteristics and other clinical characteristics (no further details reported) in the MTX arm ($\beta = 0.018$; $p = 0.003$), with no significant association in the MTX and IFX arm ($\beta = 0.004$; $p = 0.34$) (see *Table 20*). Again, baseline ESR may be prognostic for MTX but not for MTX and IFX.

Vastesaeger *et al.*[78] analysed the change from baseline in RRP (≥ 5/year in the total modified SHS score) using an ANOVA on the van der Waerden score, and presented the results of the effect of MTX and IFX versus MTX by ESR subgroup. There was a suggestion of a treatment (i.e. MTX + IFX vs. MTX) by ESR subgroup interaction. The treatment effect increased with increasing baseline ESR and was statistically significant when comparing the treatment effect in patients with baseline ESR of ≥ 52 mm/hour against the treatment effect in patients with a baseline ESR of < 21 mm/hour (difference in the treatment effects between subgroups 0.47 mm/hour, 95% CI 0.07 to 0.87 mm/hour).

Rau *et al.*[108] reported a significant correlation between ESR at baseline and Rau-modified Larsen/Sharp score for both MTX and GSTM at 6 months ($r = 0.41$, $p < 0.0001$; $r = 0.24$, $p = 0.04$, respectively) and 12 months ($r = 0.41$, $p < 0.001$; $r = 0.25$, $p < 0.03$, respectively). The association was greater in patients treated with MTX, which may indicate that baseline ESR is a treatment effect modifier.

Rau *et al.*[108] performed separate multivariable within-treatment linear regression analyses for MTX and GSTM, including covariates for tender joint count, SJC, ADL score, ESR, CRP level and RF status on radiographic change between months 0–6 and 0–12. Of these, ESR was the only statistically significant covariate (radiographic progression over 0–6 months, regression coefficient 0.49; $p = 0.001$; radiographic progression over 0–12 months, regression coefficient 0.39; $p = 0.007$) for MTX. None of the covariates was statistically significant for GSTM. Thus, ESR may be a treatment effect modifier with respect to MTX and GSTM, but it is not prognostic with respect to GSTM (scenario 3).

Prediction of treatment effect by swollen joint count at baseline: radiographic progression

Smolen *et al.*[100] reported a significant correlation between SJC at baseline and the change from baseline in SHS of > 0 for the MTX treatment arm ($r = 0.16$; $p = 0.0088$), but not for the MTX and IFX treatment arm ($r = -0.01$; $p = 0.73$). Although the association in the case of MTX is weak, the results suggest that baseline SJC may be a treatment effect modifier (i.e. it is prognostic for MTX but not for MTX and IFN). SJC at baseline was found to be significantly associated with a change in the SHS of > 0 from baseline to week 54 in separate logistic regression analyses, adjusting for baseline demographic characteristics and other clinical characteristics (no further details reported) in the MTX treatment arm ($\beta = 0.039$; $p = 0.010$), with no significant association in the MTX and IFX treatment arm ($\beta = 0.002$; $p = 0.87$). Again, baseline SJC may be a treatment effect modifier (i.e. it is prognostic for MTX but not for MTX and IFX).

Vastesaeger *et al.*[78] analysed the change from baseline in RRP (≥ 5/year in total modified SHS score) using an ANOVA on the van der Waerden score and presented the results of the effect of MTX and IFX versus MTX by 28 swollen joint count (SJC28) subgroups. There was a suggestion of a treatment (i.e. MTX and IFX vs. MTX) by SJC28 subgroup interaction; the observed treatment effects increased with increasing baseline SJC28, although these were not statistically significant.

Rau *et al.*[108] performed separate multivariable within-treatment linear regression analyses for MTX and GSTM, including covariates for tender joint count, SJC, ADL score, ESR, CRP level and RF on radiographic change between months 0–6 and 0–12. Of these, ESR was the only statistically significant covariate (radiographic progression over 0–6 months, regression-coefficient 0.49, $p = 0.001$; radiographic progression over 0–12 months, regression-coefficient 0.39, $p = 0.007$) for MTX. None of the covariates was statistically significant for GSTM. Thus, SJC was not found to be prognostic for MTX and GSTM (scenario 4).

Prediction of treatment effect by body mass index at baseline: disease activity (Disease Activity Score response)

The results from Heimans *et al.*[103] suggest that the relative risk of MTX and SSZ and tapered prednisone versus initial MTX monotherapy on treatment non-response (i.e. a DAS of > 2.4) at 1 year was greater for patients with a BMI of ≥ 25 kg/m^2 at baseline than for those with a BMI of < 25 kg/m^2 at baseline (ratio of relative risks 1.39); however, this was not statistically significant (95% CI 0.43 to 2.79). The relative risk of MTX and IFX versus initial MTX monotherapy on treatment non-response (i.e. a DAS of > 2.4) at 1 year was approximately twice that for patients with a BMI of ≥ 25 kg/m^2 at baseline compared with those with a BMI of < 25 kg/m^2 at baseline (ratio of relative risks 2.10); however, this was not statistically significant (95% CI 0.91 to 4.82).

Prediction of treatment effect by power Doppler ultrasound at baseline: radiographic progression

Taylor *et al.*[101] reported a significant correlation between the vascularity of synovium using PDUS at baseline and the change from baseline in SHS score at 54 weeks for the MTX treatment arm ($r = 0.78$; $p = 0.005$), but not for the MTX and IFX treatment arm ($r = -0.28$; $p = 0.37$). The difference in the strength of the association suggests that baseline vascularity of synovium may be a treatment effect modifier.

Discussion

Twelve primary studies were identified with which to assess the prediction of treatment response in terms of baseline covariates. Covariates examined included ACPA status, smoking status, erosions, RF status, CRP level, ESR, SJC, BMI and vascularity of synovium on PDUS. Outcomes examined included erosions/radiographic progression, disease activity, physical function and DAS28 remission.

There is no evidence, from the current review, that the end point (i.e. remission or low disease activity) had an impact on the results. One study (i.e. Huizinga *et al.*[104]) examined remission as an outcome with ACPA status as the baseline covariate, and found no significant interaction between treatment and covariate. Similarly, one study (i.e. Heimans *et al.*[103]) looked at low disease activity as an outcome, with BMI as the baseline covariate, and found no significant interaction between treatment and covariate. In order to explore the question of how end points of remission and low disease activity affect the prediction of treatment response, further research is needed to examine both end points and the same baseline covariates, preferably within the same treatment regime.

Considerable variation was found within the evidence examining the prediction of treatment response in terms of baseline covariates, in terms of covariates examined, treatments compared, outcomes assessed and statistical methodology. Most of the studies performed within-treatment analyses and examined the effects of baseline patient and/or disease characteristics using subgroup analyses, and rarely adjusted for other covariates. More importantly, no consideration was given to more flexible relationships between covariates and response and their interaction effects. It was rare for studies to perform a formal assessment of any treatment by covariate interactions; when these were performed, it is likely that the test lacked sufficient power to detect interaction effects as being statistically significant.

We have compared treatment effects across values of baseline variables in an attempt to identify potential treatment effect modifiers using data presented in the included papers (when possible). Given the heterogeneity between studies in the outcomes assessed, the differences in modelling approaches and the lack of information on the correlation between covariates, a formal quantitative synthesis of the evidence was not conducted. The conclusions were limited to a comparison between treatments at the study level and should be treated as hypothesis-generating for certain patient and/or disease characteristics being modifiers of treatment effect. Such predictors should be formally evaluated in treatment-specific clinical prediction models.

Review 2 conclusions

There was statistical evidence to suggest that ACPA status, SJC28 and PDUS status at baseline may be treatment effect modifiers, but not necessarily that they are prognostic of response for all treatments. Most of the results were subject to considerable uncertainty and were not statistically significant. In general, there was insufficient evidence that the effect of treatment depended on baseline characteristics. However, it should be noted that insufficient evidence for a covariate by treatment interaction does not mean that there is no interaction or that baseline covariates are prognostic for both treatments. The inability to reject the null hypothesis of no interaction effect is likely to reflect the power of the test being low for meaningful interaction effects.

Chapter 6 Assessment of factors relevant to the NHS and other parties

Predictors included in the clinical prediction models identified in this assessment may be useful in supplementing clinicians' decision-making regarding patient prognosis. However, because of uncertainties and limitations in the evidence base, no single clinical prediction model can currently be recommended over any other for use in clinical practice.

The prognostic factors selected for consideration in the assessment are readily available in clinical practice. However, the optimal prediction model(s) may include other biomarkers/genetic tests that are not currently available. The use of these tests may have associated practical and cost implications that will need to be considered before potential future implementation.

Collaboration between professionals within the clinical and research community would facilitate further model development and external validation research.

Chapter 7 Discussion

Statement of principal findings

Review 1 (clinical prediction models)

A total of 28 studies were identified that investigated the use of assessment tools and tests in the evaluation of prognosis in early RA patients. Twenty-two model development studies and one combined model development/external validation study reported the development and/or internal validation of a total of 39 clinical prediction models for outcomes, including radiographic joint damage, HAQ score and DAS28. Six external validation studies (including the combined model development/external validation study) were included, which tested the performance of eight clinical prediction models[57,61,69,73,76,78,79] for radiographic joint damage outcomes.

The predictive performance in internal validation was reported using the *c*-statistic in eight studies with variable results. *c*-Statistics for radiographic progression ranged between 0.63 (Degboé *et al.*[66] predicting a ΔSHS of ≥ 5 at 1 year) and 0.87 (Houseman *et al.*[72] predicting a ΔSHS of ≥ 10.5 at 8.2 years). However, many of the included models had not been externally validated. For the eight models that had been externally validated, predictive performance varied considerably. Five clinical prediction models (i.e. Syversen,[76] SWEFOT,[73] ESPOIR,[69] MBDA[61] and SONORA[57]) were externally validated in only one population per outcome. Three clinical prediction models (i.e. ASPIRE CRP,[78] ASPIRE ESR[78] and BeSt[79]) were externally validated using the same outcome definition in more than one population. The results of the RE meta-analysis indicated that the most favourable performance across external validations was for the BeSt model[79] (*c*-statistic 0.72, 95% CI 0.20 to 0.96), followed by ASPIRE ESR[78] (*c*-statistic 0.62, 95% CI 0.44 to 0.78) and ASPIRE CRP[78] (*c*-statistic 0.55, 95% CI 0.13 to 0.91). However, there is considerable heterogeneity for all three models, with the wide CIs suggesting substantial uncertainty in the expected predictive performance in a new sample of patients. The 95% CIs of the pooled estimates contain 0.5 for all three clinical prediction models, indicating that we cannot be confident that the performance of the models is better than would be expected by chance.

Limitations were observed in the methods used to develop the included clinical prediction models, such as the absence of potentially important candidate predictors and the incorrect handling of continuous predictors. For models developed using RCT data with patients assigned to alternative treatment strategies, the model development generally failed to assess the interactions between predictors and treatment group, and so did not generate truly treatment-specific models.

There was no evidence to suggest that a single clinical prediction model performs well in all patients. Further research is required to determine the optimal clinical prediction model(s) for use in clinical practice and to determine the value of any emerging, currently untested candidate predictors in the development of future prediction models.

Review 2 (prediction of treatment response)

Twelve primary studies were identified with which to assess the prediction of treatment response according to baseline covariates. Covariates examined included ACPA status, smoking status, erosions, RF status, CRP level, ESR, SJC, BMI and vascularity of synovium on PDUS. Outcomes examined included erosions/radiographic progression, disease activity, physical function and DAS28 remission.

There was statistical evidence to suggest that ACPA status, SJC28 and PDUS status at baseline may be treatment effect modifiers, but not necessarily that they are prognostic of response for all treatments. Most of the results were subject to considerable uncertainty and were not statistically significant. In general, there was insufficient evidence that the effect of treatment depended on baseline characteristics.

Strengths and limitations of the assessment

This assessment has been undertaken according to current good practice in prognostic systematic reviews.[26,48,118] A comprehensive range of predictors readily available in clinical practice and key outcomes were selected for review. However, in order to maintain the feasibility of the assessment within the resources and time scales available, a limited number of protocol amendments were necessary, as described in *Appendix 2*. It was also necessary to limit the inclusion of studies to those published in the English language, because resources were not available to allow for the translation of non-English-language articles.

The evaluation of prognostic models and the evidence regarding differential treatment effects according to different values of predictor variables was limited to published aggregate data; published models typically involved different predictor variables and did not include interaction terms with treatment. In both cases, the ideal scenario would be to fit common models to the IPD. Access to IPD would allow harmonisation (both in terms of model development and validation). However, analyses using IPD were beyond the scope of this assessment.

Uncertainties

Despite the availability of a range of clinical prediction models, uncertainty remains over which (if any) is the most appropriate for use in clinical practice. In order to assess the comparative performance of the competing models more thoroughly, further external validations would be required. However, limitations were observed in the methods used to develop the clinical prediction models. It is therefore likely that the most clinically useful prediction model would contain predictors from across more than one of the reviewed clinical prediction models and would consider alternative handling of key predictive variables. Interactions between predictors and treatment group were rarely considered, and so there is limited evidence regarding differential treatment effects according to different values of predictor variables.

Future research should seek to demonstrate the predictive value of existing variables that are currently included in available clinical prediction models and should also aim to identify new, potentially valuable variables for testing in future clinical prediction models. The development of new clinical prediction models should conform to recommended good practice in model development and reporting (e.g. adherence to the TRIPOD statement). Developed models should be externally validated in order to demonstrate their usefulness. External validations should be conducted in clinically appropriate populations with previously untreated early RA, and with sufficient variation (or case mix) in the population to ensure that the results are generalisable to the target clinical population.

Chapter 8 Conclusions

Implications for service provision

Review 1: clinical prediction models

No single clinical prediction model can currently be recommended in preference to any other model for use in clinical practice because of uncertainties and limitations in the existing evidence base. The optimal prediction model(s) may include variables (e.g. biomarkers/genetic tests) that are not routinely or currently available. Their potential use may have associated practical and cost implications that will need to be evaluated before future implementation.

Review 2: prediction of treatment response

There was limited evidence with which to assess whether or not specific baseline variables can predict differential effects according to the treatment administered. Nevertheless, the available evidence suggested that some baseline variables do affect relative treatment effects and that not all baseline variables may be prognostic of response for all treatments.

There was statistical evidence to suggest that ACPA status, SJC28 and PDUS status at baseline may be treatment effect modifiers, but not necessarily that these are prognostic of response for all treatments. Most of the results were subject to considerable uncertainty and were not statistically significant.

In general, there was insufficient evidence that the effect of treatment depended on baseline characteristics. This may be a real effect or may be because studies lacked statistical power to detect interaction effects. The true effect of baseline variables should be evaluated in single multivariable models adjusting for all relevant confounders.

Suggested research priorities

Review 1: clinical prediction models

- Collaborative research, including the use of IPD, for further (1) development/internal validation and (2) external validation of clinical prediction model(s) with improved predictive performance.
- Adherence to good reporting standards of future clinical prediction model studies (e.g. in accordance with the TRIPOD statement[26]).

Review 2: prediction of treatment response

- Clinical prediction models should be developed and validated with respect to individual treatments.
- The assessment of treatment by covariate interactions should follow good statistical practice: subgroup analyses should be avoided; categorising continuous baseline covariates should be avoided; and the interactions between treatments and baseline variables should be specifically modelled.
- The results of multivariable analyses presented in published reports should include estimates of the main effects of covariates and any interaction effects, together with their standard errors and covariances for secondary research purposes.

Acknowledgements

We would like to thank Dr Frank McKenna (Consultant Rheumatologist, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK) and Dr Patrick Kiely (Consultant Rheumatologist, St George's University Hospitals NHS Foundation Trust, London, UK) for providing clinical advice. The team would also like to acknowledge the input of two patient and public involvement representatives in providing comments on the plain English summary and the draft assessment report. We thank Gill Rooney (Programme Manager, School of Health and Related Research, University of Sheffield, Sheffield, UK) for providing administrative support and for preparing and formatting the report. We would like to thank Robert Wolff for sharing an unpublished version of the PROBAST quality assessment tool. We would also like to thank Diederik De Cock for responding to queries relating to his published study.

About the School of Health and Related Research

The School of Health and Related Research (ScHARR) is one of the twelve departments that comprise the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the NIHR HTA programme on behalf of a range of policy-makers, including the National Institute for Health and Care Excellence (NICE). ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen HTA Group, University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE), University of York; Warwick Evidence, University of Warwick; the BMJ Group and Kleijnen Systematic Reviews.

Contributions of authors

Rachel Archer (Research Fellow; area of specialty: systematic reviewing) was the lead for the overall assessment and the lead systematic reviewer for review 1.

Emma Hock (Research Fellow; area of specialty: systematic reviewing) was the lead systematic reviewer for review 2.

Jean Hamilton (Research Fellow; area of specialty: statistical methods in health economics) was involved in study selection, the checking of data extraction, data analysis and interpretation and performing the meta-analysis of external validation studies in review 1, and provided statistical advice to the overall assessment.

John Stevens (Reader in Decision Science; area of specialty: medical statistics and evidence synthesis) was involved in study selection, data analysis and the interpretation of results for review 2, and provided statistical advice to the overall assessment.

Munira Essat (Research Fellow; area of specialty: systematic reviewing) and **Edith Poku** (Research Fellow; area of specialty: systematic reviewing and evidence-based medicine) were involved with the double-checking of the extracted data and the quality assessment results for reviews 1 and 2.

Mark Clowes (Information Specialist; area of specialty: information retrieval) performed the scoping and full searches.

Abdullah Pandor (Senior Research Fellow, area of specialty: systematic reviewing) and **Matt Stevenson** (Professor of Health Technology Assessment; area of specialty: HTA) provided advice on the methods and conduct of the assessment.

All authors were involved in drafting and commenting on the final report.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Appendix 1 Additional details of the scoping of the assessment

Appropriate methods for the identification of prognostic and predictive studies were considered by the review team. Although various filters are available, published validation studies suggested that none of these can be completely relied on.[119,120] Therefore, the review team consulted the website of the Cochrane Prognosis Methods Group [http://methods.cochrane.org/prognosis/our-publications (accessed July 2016)] and judged that the 'sensitivity-maximising' search strategies, devised by the Hedges' team at McMaster University for identifying prognostic and clinical prediction studies, would be most suitable for use in this assessment.[44,53]

The initial phase 1 scoping searches of MEDLINE were conducted to assess the size of the available literature. The numbers of results retrieved were multiplied by 2.5 for an approximate estimate of the total numbers to be found across other databases. The search terms for RA were initially combined with the Hedges' team filter to retrieve as broad as possible a set of prognostic studies. This was estimated to yield approximately 40,000 records, if the searches were extended to all included databases.

According to a validation study by Geersing *et al.*,[120] the Haynes' filter results in a very low number of missed studies; however, Geersing *et al.*[120] recommended its use for scoping purposes only, suggesting that, if a review is interested in only one or two specific variables, it is best to search for these without the application of any filter.

Potential candidate prognostic and predictive variables were identified to inform discussion with clinical experts.

A separate methodological exercise was undertaken to examine a sample of the records that were retrieved by the Haynes' filter but did not contain any of the terms relating to our candidate variables. The free-data visualisation tool VOSviewer version 1.6.5 (Centre for Science and Technology Studies, Leiden University, the Netherlands)[121] was used to display frequently occurring words and phrases in a sample of the discarded records in an attempt to reveal any emerging variables that were unknown to the team. No new potential candidate variables for discussion were revealed through this process.

Following discussions with two expert clinical advisors who manage patients with early RA in the UK (see *Acknowledgements*), the review team selected variables for inclusion based on:

- tests and assessment tools (e.g. selected laboratory tests, imaging tests and clinical assessment measures) being readily available and used in UK clinical practice (and, therefore, genetic markers were not included by the review team)
- the clinical experience of advisors in evaluating prognosis/treatment response in patients
- the initial scoping of literature in the area by the review team.

Appendix 2 Additional details of deviations from the final protocol

Review 1

- It was anticipated that, in the final protocol, the study types included in review 1 would probably include published reports of cohort studies (and potentially case–control studies) that report the associations between individual prognostic variables and outcomes. In order to maintain the feasibility of the assessment, review 1 was restricted to the inclusion of studies that describe the development, external validation or impact of eligible clinical prediction models in early RA. Therefore, in line with the multivariable approach employed in prediction model research, individual prognostic factors were not studied.
- It was necessary, because of resource and time constraints, to adopt an iterative approach to the screening of evidence during the review 1 study selection (as described in *Chapter 3*, *Study selection*). It was also originally intended in the final protocol that a randomly selected sample of titles/abstracts would be checked by a second reviewer. However, in light of the iterative screening approach applied in review 1, it was no longer considered appropriate to undertake this stage.
- It was originally intended in the final protocol that all studies would be assessed by criteria informed by the QUIPS tool.[54] However, it was necessary to revise this approach in order to allow for the quality assessment of the included clinical prediction model and external validation studies using the most methodologically appropriate tool (PROBAST).[49]
- It was stated in the review protocol that meta-analyses would be conducted using a Bayesian RE model. However, this was modified for the final analysis because there were very few studies that validated each clinical prediction model, thereby providing limited information with which to estimate the between-study heterogeneity. Although it would be possible to implement a Bayesian RE analysis using a weakly informative prior, this was not implemented because there was a lack of empirical evidence to inform the prior distribution for the heterogeneity parameter and eliciting experts' beliefs was beyond the scope of this project. Although the analysis deviated slightly from the protocol, the implemented RE model accounts for uncertainty in the between-study heterogeneity and is consistent with the methodological recommendations.[40]

Review 2

Following a protocol amendment, to maintain the feasibility of the assessment, review 2 comprised:

- a systematic review of studies that describe the development, external validation or impact of eligible clinical prediction models to predict the response to individual treatments in patients with early RA (developed/validated in observational cohorts or experimental data sets)
- a review of primary studies (experimental or observational) to identify patient characteristics that affect the response to individual treatments in patients with early RA.

Appendix 3 Sample search strategy (MEDLINE)

Database: Ovid MEDLINE (R) Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, Ovid MEDLINE and Versions (R).

Date range searched: 1947 to September 2016.

Date searched: 27 September 2016.

Search strategy

1. exp rheumatoid arthritis/ (101,628)
2. rheumatoid arthritis.tw. (89,399)
3. 1 or 2 (129,354)
4. incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos:.tw. or predict:.tw. or course:.tw. (2,798,958)
5. exp animals/ not exp humans/ (4,320,871)
6. 4 not 5 (2,590,653)
7. predict:.mp. or scor:.tw. or observ:.mp. (4,442,632)
8. 7 not 5 (3,608,545)
9. 3 and 6 (17,646)
10. (3 and 8) not 9 (17,584)
11. (ACPA or ACPAs or anti-CCP* or antiCCP* or anti-CPA or antiCPA or ACCP*).mp. (3078)
12. (anti-cyclic citrullinated or anticyclic citrullinated).mp. (1271)
13. (anticitrullinated or anti-citrullinated).mp. (924)
14. 11 or 12 or 13 (3733)
15. (rheumat* factor* or RF).mp. (38,768)
16. exp radiography/ (707,925)
17. (radiologic* or radiograph* or x-ray* or xray*).mp. (1,010,600)
18. ((erosi* or erode*) adj3 (bone* or joint*)).mp. (3790)
19. erosion progression.mp. (57)
20. sharp score.mp. (340)
21. joint space narrowing.mp. (1373)
22. JSN.mp. (405)
23. 16 or 17 or 18 or 19 or 20 or 21 or 22 (1,262,189)
24. (disease activity score or DAS).mp. (51,082)
25. (28 joint* or twenty eight joint*).mp. (1665)
26. 24 and 25 (1509)
27. (DAS28 or DAS 28).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2897)
28. 26 or 27 (3287)
29. (ESR or (erythrocyte* adj3 sediment*)).mp. or erythrocyte sedimentation rate/ (30,112)
30. C-Reactive Protein/ or (c reactive protein* or CRP or C-RP).mp. (699,592)
31. (SJC or (sw#ll* adj3 joint* adj2 (count* or number*))).mp. (1375)
32. 28 or 29 or 30 or 31 (94,961)
33. (smok* or tobacco or nicotine or cigarette* or ecig* or vape*).mp. (335,894)
34. Delayed Diagnosis/ (3879)
35. ((late or delay*) adj3 (treat* or present* or diagnos* or help-seeking or visit* or doctor* or GP* or report* or consult* or assess*)).mp. (70,970)
36. ("time to presentation" or untreated or un-treated).mp. (154,236)

37. disease duration.mp. (14,321)
38. 34 or 35 or 36 or 37 (250,927)
39. (BMI or body mass ind* or obes* or overweight or over-weight).mp. (410,712)
40. haq* or health assessment questionnaire*).mp. (4175)
41. exp ultrasonography/ (280,410)
42. (ultrasound or ultrasonogra* or sonogra* or doppler).mp. (408,038)
43. 41 or 42 (495,613)
44. exp Antirheumatic Agents/ (384,372)
45. (Disease-modifying antirheumatic* or Disease-modifying anti-rheumatic*).mp. (4245)
46. DMARD* or bDMARD* or cDMARD*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3486)
47. exp Biological Therapy/ or biological therap*.mp. (395,939)
48. (biologic or biologics).mp. (57,465)
49. ciclosporin or cyclosporine or cyclophosphamide or cytophosphane or (gold adj2 (inject* or intraven*)) or myocrisin or sodium aurothiomalate or gold sodium thiomolate or hydroxychloroquine or HCQ or Plaquenil or leflunomide or arava or methotrexate or amethopterin or mycophenolate or Mycophenolic acid or CellCept or Myfortic or sulfasalazine or sulphasalazine or salazopyrin or sulazine or azulfidine or abatacept or CTLA41g or orencia or rituximab or mabthera or tocilizumab or Actemra or RoActemra or adalimumab or humira or certolizumab pegol or cimzia or etanercept or enbrel or golimumab or simponi or infliximab or remicade).af. (187,989)
50. (anti-TNF or antiTNF or ((TNF* or tumo?r necros#s factor*) adj3 (inhibit* or block* or antagonist* or anti* or alpha)) or interleukin 1 or IL-1 or monoclonal antibod* or costimulation blocker* or co-stimulation blocker* or interleukin 6 or IL-6 or ("T lymphocyt*" adj2 activat*) or B lymphocyt* or Biosimilar*).mp. (525,731)
51. (adalimumab or humira or d 2e7 or d2e7).af. or 331731-18-1.rn. or etanercept.af. or enbrel.af. or 185243-69-0.rn. or infliximab.af. or remicade.af. or 170277-31-3.rn. or ta650.af. or ta 650.af. or certolizumab pegol.af. or cimzia.af. or cdp870.af. or 428863-50-7.rn. or 1132819-27-2.rn. or czp.af. or abatacept.af. (20,564)
52. (orencia or 213252-14-3 or 332348-12-6 or bms188667 or bms 188667 or ctla4ig or ctla 4ig or golimumab or cnto148 or cnto 148 or simponi or 476181-74-5 or tocilizumab or atlizumab or actemra or roactemra or 375823-41-9 or tofacitinib or xeljanz or tasocitinib or cp690550 or cp 690550 or 540737-29-9 or rituximab or rituxan or mabthera).af. or 174722-31-7.rn. (19,971)
53. atacicept.af. or 845264-92-8.rn. or unii-k3d9a0icq3.af. or uniik3d9a0icq3.af. or taci-fc5.af. or tacifc5.af. or taci-ig.af. or taciig.af. (107)
54. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (1,313,135)
55. 14 or 15 or 23 or 32 or 33 or 38 or 39 or 40 (2,253,817)
56. 9 and 55 (7258)
57. limit 56 to english language (6321)
58. 55 or 43 (2,627,621)
59. 3 and 8 and 58 (12,425)
60. 54 and 59 (5264)
61. limit 60 to english language (4943)

Appendix 4 Review 1 excluded full-text studies

TABLE 21 Review 1 excluded full-text studies with rationale

First author (date of publication)	Title of publication	Justification for exclusion
Akhavan (2011)[122]	Prevalence of and predictive factors for sustained remission in early RA: results from SONORA study	No measure of predictive performance reported
Alemao (2014)[123]	Development and validation of a prognostic clinical model for rapid radiographic progression in patients with RA	Not early RA
Aletaha (2013)[124]	Rheumatoid factor determines structural progression in rheumatoid arthritis dependent and independent of disease activity	No measure of predictive performance reported
Alishiri (2008)[125]	Logistic regression models for predicting physical and mental health-related quality of life in rheumatoid arthritis patients	Not early RA
Allaart (2011)[126]	A multi-biomarker disease activity (Vectra DA) algorithm score for rheumatoid arthritis predicts radiographic progression in the BeSt study	Preliminary report. No further relevant data reported
Alves (2010)[127]	The ACR/EULAR 2010 criteria as well as other predictive algorithms for rheumatoid arthritis show good diagnostic performance	Study design
Anderson (2000)[128]	Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration	Study design
Balsa (2010)[129]	Prediction of functional impairment and remission in rheumatoid arthritis patients by biochemical variables and genetic polymorphisms	Not early RA
Bakker (2010)[130]	Development of a multi-biomarker test for rheumatoid arthritis (RA) disease activity (Vectra DA)	Preliminary report. No further relevant data reported
Bakker (2012)[131]	Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study	No measure of predictive performance reported for radiographic progression. Associations with DAS28 reported (not used in prediction)
Barnabe (2014)[132]	Socio-demographic and health status characteristics explain clinical outcome trajectories in early inflammatory arthritis (EIA)	Conference abstract with no definition of early RA. Early inflammatory arthritis
Bedran (2013)[133]	Validation of a prediction rule for the diagnosis of rheumatoid arthritis in patients with recent onset undifferentiated arthritis	Diagnostic study
Belghomari (1999)[134]	Risk factors for radiographic articular destruction of hands and wrists in rheumatoid arthritis	Study design
Bombardier (2009)[135]	Which subgroups are at higher risk of rapid radiographic progression in early rheumatoid arthritis: results from SONORA study	Not handled as primary report of SONORA radiographic risk model

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Bombardier (2010)[136]	Radiographic damage and radiographic progression are predictors for physical function: results from SONORA study	Limited reporting and no measure of predictive performance
Bombardier (2010)[137]	Sustained remission in early RA: results from SONORA study	Limited reporting and no measure of predictive performance
Bombardier (2010)[138]	Clinical prognostic factors for radiographic damage in early rheumatoid arthritis: results from SONORA study	Not handled as primary report of SONORA radiographic risk model
Bøyesen (2009)[139]	Antibodies to cyclic citrullinated protein and erythrocyte sedimentation rate predict hand bone loss in patients with rheumatoid arthritis of short duration: a longitudinal study	Study design
Breedveld (2004)[140]	Multiple faces of rheumatoid arthritis: diagnostic and therapeutic algorithms	Study design
Britsemmer (2011)[141]	Validation of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: slight improvement over the 1987 ACR criteria	Study design
Brown (2007)[142]	Serum macrophage inhibitory cytokine 1 in rheumatoid arthritis: a potential marker of erosive joint destruction	Not early RA
Bruynesteyn (2002)[143]	Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence	Study design
Bukhari (2002)[144]	Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis: results from the Norfolk Arthritis Register Study, a large inception cohort	No measure of predictive performance reported
Carrier (2016)[145]	Serum levels of 14-3-3η protein supplement C-reactive protein and rheumatoid arthritis-associated antibodies to predict clinical and radiographic outcomes in a prospective cohort of patients with recent-onset inflammatory polyarthritis	No measure of predictive performance reported
Caruso (1990)[146]	Clinical, laboratory and radiographic features in early rheumatoid arthritis	No measure of predictive performance reported
Chalan (2013)[147]	Circulating CD4+CD161+ T lymphocytes are increased in seropositive arthralgia patients but decreased in patients with newly diagnosed rheumatoid arthritis	No prognostic/predictive factors under assessment
Chibnik (2011)[148]	Genetic risk score predicting risk of rheumatoid arthritis phenotypes and age of symptom onset	Unclear reporting of duration of disease at baseline
Ciurtin (2016)[149]	Ultrasound-detected subclinical inflammation was better reflected by the disease activity score (DAS-28) in patients with suspicion of inflammatory arthritis compared to established rheumatoid arthritis	Not early RA
Conaghan (2010)[150]	Persistently moderate DAS28 is not benign: loss of function occurs in early RA despite step-up DMARD therapy	Study design
Conaghan (2011)[151]	Predicting outcomes in rheumatoid arthritis	Literature review

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Corbett (1988)[152]	The Middlesex hospital prospective study of early rheumatoid disease	Insufficient details available on population characteristics and methods
Corbett (1993)[153]	Factors predicting death, survival and functional outcome in a prospective study of early rheumatoid disease over fifteen years	Not eligible outcome
Courvoisier (2008)[154]	Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study	No measure of predictive performance reported
Curtis (2010)[155]	Validation of a multi-biomarker test for rheumatoid arthritis (RA) disease activity (Vectra DA) in a multi-cohort study	Preliminary report of Curtis *et al.*[156]
Curtis (2012)[156]	Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity	Symptom duration at baseline not reported
Curtis (2015)[157]	A randomized trial comparing disease activity measures for the assessment and prediction of response in rheumatoid arthritis patients initiating certolizumab pegol	Not early RA
Dawes (1986)[158]	Prediction of progressive joint damage in patients with rheumatoid arthritis receiving gold or D-penicillamine therapy	Duration of symptoms for total group not reported, but data available indicate not early RA
de Carvalho (1980)[159]	Radiographic progression of rheumatoid arthritis related to some clinical and laboratory parameters	Study design
de Punder (2015)[160]	Personalising treatment targets in rheumatoid arthritis by using a simple prediction model	Prediction model includes variables measured outside early RA definition
de Vries-Bouwstra (2008)[161]	Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies	No measure of predictive performance reported
Desai (2015)[162]	An external validation study reporting poor correlation between the claims-based index for rheumatoid arthritis severity and the disease activity score	Duration of symptoms not reported
Eastman (2012)[163]	Characterisation of a multiplex, 12-biomarker test for rheumatoid arthritis	Study design
Eberhardt (1990)[164]	Early rheumatoid arthritis – onset, course and outcome over 2 years	Limited reporting of predictive performance
Eberhardt (1996)[165]	Associations of *HLA-DRB* and *-DBQ* genes with two and 5 year outcome in rheumatoid arthritis	Not eligible factor
Elshafie (2013)[166]	IgA rheumatoid factor is more predominant than anti-CCP in Sudanese rheumatoid arthritis patients, whereas IgG RF is a strong prognostic marker and associated with early onset	Study design
Emery (1996)[167]	Algorithm to predict radiological erosions in early rheumatoid arthritis. Messages from paper are incorrect	Letter to editor

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Emery (2008)[168]	Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis	Review
Forslind (2007)[169]	Sex: a major predictor of remission in early rheumatoid arthritis?	No measure of predictive performance reported
Fautrel (2011)[170]	Identification of patients who could require early biologic therapy by developing a matrix predicting rapid radiographic progression in early rheumatoid arthritis patients treated by methotrexate. A study based on the ESPOIR cohort data	Preliminary report of included study. No further relevant data reported
Fautrel (2012)[171]	Value of matrices developed to identify early rheumatoid arthritis patients with rapid radiographic progression despite methotrexate therapy: a comparison of their performance in the early rheumatoid arthritis ESPOIR cohort	Preliminary report of included study. No further relevant data reported
Fautrel (2013)[172]	Performance of rapid radiographic progression prediction matrices in the early rheumatoid arthritis patients of the ESPOIR cohort	Preliminary report of included study. No further relevant data reported
Fautrel (2015)[173]	Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment	Not early RA
Fransen (2010)[174]	Validity of the revised ACR/EULAR classification criteria for rheumatoid arthritis: predicting persistent arthritis and joint erosions after 2 years in patients with early undifferentiated arthritis	Diagnostic study
Gardiner (2015)[175]	Estimating under-diagnosis of rheumatoid arthritis in primary care data from the UK clinical practice research datalink	Diagnostic study
Garnero (2002)[102]	Association of baseline levels of urinary glucosyl-galactosyl-pyridinoline and type II collagen C-telopeptide with progression of joint destruction in patients with early rheumatoid arthritis	No measure of predictive performance reported
Goronzy (2004)[176]	Prognostic markers of radiographic progression in early rheumatoid arthritis	No measure of predictive performance reported
Graudal (2004)[177]	The natural history and prognosis of rheumatoid arthritis: association of radiographic outcome with process variables, joint motion and immune proteins	Not eligible risk model with measure of predictive performance
Graudal (2004)[178]	Scandinavian Journal of Rheumatology: preface	No further data to Graudal *et al.*[177]
Green (2003)[179]	Serum MMP-3 and MMP-1 and progression of joint damage in early rheumatoid arthritis	Limited reporting of predictive performance
Haji (2012)[180]	Can sustained remission of rheumatoid arthritis be predicted? An analysis from the Japanese national database of rheumatic disease (NinJa)	Disease duration at baseline not reported
Haji (2013)[181]	A prediction rule for sustained remission of rheumatoid arthritis	Disease duration at baseline not reported

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Hambardzumyan (2013)[182]	A multi-biomarker disease activity blood test (Vectra DA) correlates with radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial	Preliminary report of included study. No further relevant data reported
Hambardzumyan (2013)[183]	A multi-biomarker disease activity score correlates with radiographic progression in early rheumatoid arthritis: results from a randomised trial	Preliminary report of included study. No further relevant data reported
Hambardzumyan (2013)[184]	Multi-biomarker disease activity (MBDA) score and the 12 individual biomarkers in early rheumatoid arthritis patients relate differentially to clinical response and radiographic progression: results from the SWEFOT trial	Preliminary report of included study. No further relevant data reported
Hambardzumyan (2013)[185]	In early rheumatoid arthritis, the 12 individual biomarkers that comprise the multiple biomarker disease activity score relate differentially to clinical response and radiographic progression: results from a randomised trial	Preliminary report of included study. No further relevant data reported
Harrison (1999)[186]	The influence of HLA-DRB1 alleles and rheumatoid factor on disease outcome in an inception cohort of patients with early inflammatory arthritis	Study design
Harrison (2001)[187]	The association of cigarette smoking with disease outcome in patients with early inflammatory polyarthritis	Mixed arthritis population (< 80% were people with RA) and no subgroup. No measure of predictive performance reported
Hazes (2011)[188]	The epidemiology of early inflammatory arthritis	Literature review
Heimans 2014[91]	A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study	Study design
Hendrikx (2013)[189]	Moving towards personalized healthcare: a patient reported outcome based algorithm can aid rheumatologists and patients in monitoring rheumatoid arthritis in daily clinical practice	Study design
Hendrikx (2015)[190]	Monitoring rheumatoid arthritis using an algorithm based on patient-reported outcome measures: a first step towards personalised healthcare	Study design
Hirata (2013)[191]	A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study	Outcome measurement time point unclear
Hirata (2016)[192]	Assessment of disease activity in rheumatoid arthritis by multi-biomarker disease activity (MBDA) score	Full text not in the English language
Houssien (1998)[193]	Rheumatoid factor isotypes, disease activity and the outcome of rheumatoid arthritis: comparative effects of different antigens	Not early RA. Study design
James (2004)[194]	Orthopaedic intervention in early rheumatoid arthritis. Occurrence and predictive factors in an inception cohort and 1064 patients followed for 5 years	Not eligible outcome. Study design

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Jessome (2014)[195]	Assessing the validity and reliability of a novel MRI semi-automated algorithm for quantifying bone loss in the hand	Study design
Jessome (2015)[196]	Early erosions in rheumatoid arthritis (EERA) software reliably measures erosive damage on MRI in the metacarpophalangeal joints of rheumatoid arthritis patients	Study design
Kaarela (1985)[197]	Prognostic factors and diagnostic criteria in early rheumatoid arthritis	Mixed early arthritis population and diagnostic focus of study
Kapoor (2013)[198]	The impact of inflammation on metabolomic profiles in patients with arthritis	Study design
Kastbom (2016)[199]	Changes in the anticitrullinated peptide antibody response in relation to therapeutic outcome in early rheumatoid arthritis: results from the SWEFOT trial	No measure of predictive performance
Kaufmann (2013)[200]	Comparison between several prediction scores and the new EULAR/ACR criteria for diagnosis and prognosis of rheumatoid arthritis	Study design. Comparison of criteria for development of RA in early arthritis cohort
Keller (1999)[201]	The SF-36 Arthritis-Specific Health Index (ASHI): II. Tests of validity in four clinical trials	Study design
Kent (2009)[202]	Analysis of multiple phenotypes	Literature review
Kirino (2015)[203]	Predicting joint destruction in rheumatoid arthritis with power Doppler, anti-citrullinated peptide antibody, and joint swelling	Not early RA
Kita (2010)[204]	MRI-proven bone edema of wrist and finger joints at entry is the strongest predictor toward further radiographic progression in patients with undifferentiated arthritis: results from the prospective cohort at Nagasaki university	Insufficient results reported
Knudsen (2008)[205]	Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome	Study design
Kojima (2015)[206]	Patient-reported outcomes as assessment tools and predictors of long-term prognosis: a 7-year follow-up study of patients with rheumatoid arthritis	Not early RA
Kokebie (2010)[207]	The role of synovial fluid markers of catabolism and anabolism in osteoarthritis, rheumatoid arthritis and asymptomatic organ donors	Study design
Kooloos WM, Huizinga TWJ, Guchelaar HJ, Klareskog L, Padyukov L, Wessels JAM, van Vollenhoven RF. Department of Clinical Pharmacy and Toxicology, and Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; 2009	External validation of the clinical pharmacogenetic model for predicting MTX monotherapy efficacy using a Swedish cohort of patients with recent-onset rheumatoid arthritis	Not eligible outcome

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Krabben (2013)[208]	Risk of rheumatoid arthritis development in patients with unclassified arthritis according to the 2010 ACR/EULAR criteria for rheumatoid arthritis	Not early RA. Study evaluating progression to RA in unclassified arthritis cohort
Kroot (2000)[209]	The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis	Limited reporting of predictive performance
Kvien (2000)[210]	Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis	Not early RA
Lahiri (2014)[211]	Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register-the EPIC-2-NOAR Study)	Not eligible end point. Risk of developing inflammatory polyarthritis or RA
Lahiri (2013)[212]	A risk score to identify individuals at higher risk of inflammatory polyarthritis: results from the European prospective investigation of cancer (Norfolk) and the Norfolk arthritis register (the EPIC-2-NOAR study)	Not eligible end point. Risk of developing inflammatory polyarthritis or RA
Landewe (2007)[213]	Predictive markers in rapidly progressing rheumatoid arthritis	Review
Lanfant (2008)[214]	An algorithm including the intrasynovial expression of CD20 and serum biomarkers (rheumatoid factors, anti-CCP2 and RANK-ligand) able to predict the progression of bone erosions in very early arthritis	Insufficient details reported
Lanfant-Weybel (2012)[215]	Synovium CD20 expression is a potential new predictor of bone erosion progression in very early arthritis treated by sequential DMARDs monotherapy – a pilot study from the VErA cohort	Study design
Lauwerys (2015)[216]	Heterogeneity of synovial molecular patterns in patients with arthritis	Study design
Le Loët (2010)[217]	Serum IgA rheumatoid factor and pyridinoline in very early arthritis as predictors of erosion(s) at two years: a simple model of prediction from a conservatively treated community-based inception cohort	Study design. Study population: $\leq$ 80% with RA
Li (2016)[218]	Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis	Not early RA
Li (2013)[219]	Biomarker-based estimates of risk of radiographic progression in the Leiden early arthritis cohort	Conference abstract of Li *et al.*[218]
Li (2013)[220]	Impact of a multi-biomarker disease activity test on rheumatoid arthritis treatment decisions and therapy use	Not available
Liao (2009)[221]	Clinical factors that predict erosion-free status in rheumatoid arthritis	Not early RA

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Liao 2011[222]	Clinical predictors of erosion-free status in rheumatoid arthritis: a prospective cohort study	Available data indicate not early RA
Lillegraven (2013)[223]	The performance of matrix-based risk models for rapid radiographic progression in an observational cohort of established rheumatoid arthritis patients	External validation cohort not early RA
Lillegraven (2013)[95]	Performance of matrix-based risk models for rapid radiographic progression in a cohort of patients with established rheumatoid arthritis	External validation cohort not early RA
Lindqvist (2002)[224]	Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage	Limited reporting of predictive performance
Lindqvist (2005)[225]	Prognostic laboratory markers of joint damage in rheumatoid arthritis	No measure of predictive performance reported
Linn-Rasker (2007)[226]	Arthritis of the large joints – in particular, the knee, at first presentation is predictive for a high level of radiological destruction of the small joints in rheumatoid arthritis	No measure of predictive performance reported
Lisitsyna (2014)[227]	Factors associated with major depressive disorder in rheumatoid arthritis patients	No eligible end point
Lisitsyna (2015)[228]	Depression as a risk factor for joints destruction in rheumatoid arthritis patients	Insufficient details reported
Liu (2009)[229]	Prediction of disease severity in patients with early rheumatoid arthritis by gene expression profiling	Study design
Løppenthin (2015)[230]	Physical activity and the association with fatigue and sleep in Danish patients with rheumatoid arthritis	Not early RA
Luukkainen (1983)[231]	The prediction of radiological destruction during the early stage of rheumatoid arthritis	Not available
Ma (2014)[232]	Multi-biomarker disease activity score is associated with Power Doppler ultrasound in patients with rheumatoid arthritis in low disease activity state	Duration of RA at baseline not reported
Ma (2012)[233]	Biomarker signature in rheumatoid arthritis patients with low disease activity: the REMIRA study	Not available
Ma (2011)[234]	Investigation of a multi-biomarker disease activity (Vectra DA) signature and algorithm score in rheumatoid arthritis patients with low disease activity: the REMIRA study	Not early RA
Ma (2014)[235]	Clinical and serological predictors of remission in rheumatoid arthritis are dependent on treatment regimen	Insufficient reporting of predictive performance
Ma (2012)[236]	Remission in early rheumatoid arthritis: predicting treatment response	No eligible factor included in final model
Machold (2007)[237]	Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease	Limited reporting of predictive performance

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Mamehara (2010)[238]	Serum matrix metalloproteinase-3 as predictor of joint destruction in rheumatoid arthritis, treated with non-biological disease modifying anti-rheumatic drugs	Not early RA
Mathsson (2008)[239]	Antibodies against citrullinated vimentin in rheumatoid arthritis	Not eligible risk model with measure of predictive performance
Mei (2007)[240]	Evaluating gene × gene and gene × smoking interaction in rheumatoid arthritis using candidate genes in GAW15	Study design
Miller (2013)[241]	The diagnostic accuracy of rheumatoid factor testing in primary care	Diagnostic study
Miller (2014)[242]	Negative rheumatoid factor in primary care delays referral of patients with rheumatoid arthritis	Study design
Mierau (2006)[243]	Diagnosis and prognosis of early rheumatoid arthritis, with special emphasis on laboratory analysis	Review
Möller (2014)[244]	Anaemia may add information to standardised disease activity assessment to predict radiographic damage in rheumatoid arthritis: a prospective cohort study	Duration of symptoms at baseline not reported for total population but available data indicate not early RA
Morel (2005)[245]	How to predict prognosis in early rheumatoid arthritis	Review
Möttönen (1988)[246]	Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis	Limited reporting of predictive performance
Möttönen (1998)[247]	Only high disease activity and positive rheumatoid factor indicate poor prognosis in patients with early rheumatoid arthritis	No measure of predictive performance reported
Nakashima (2016)[248]	Magnetic resonance imaging bone oedema at enrolment predicts rapid radiographic progression in patients with early RA: results from the Nagasaki University early arthritis cohort	Unclear reporting of predictive performance
Nell (2005)[249]	Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis	Limited reporting of predictive performance
Nielen (2005)[250]	Antibodies to citrullinated human fibrinogen (ACF) have diagnostic and prognostic value in early arthritis	Mixed population. Available data indicate that < 80% of the study population had RA and no early RA subgroup
Nishiguchi (2014)[251]	Self-assessment tool of disease activity of rheumatoid arthritis by using a smartphone application	Study design
Nishiguchi (2016)[252]	Self-assessment of rheumatoid arthritis disease activity using a smartphone application. Development and 3-month feasibility study	Study design
Norton (2013)[253]	Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality	No measure of predictive performance reported

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Norton (2013)[254]	A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome	Not eligible risk model with measure of predictive performance
Norton (2014)[255]	Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts	No measure of predictive performance
Ødegård (2006) [256]	Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients	Not early RA
Papadopoulos (2005)[257]	Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis?	No measure of predictive performance reported
Park (2011)[258]	Patterns of radiographic outcomes in early, seropositive rheumatoid arthritis: a baseline analysis	Study design
Park (2014)[259]	Examining radiographic outcomes over time	Study design
Plant (1994)[260]	Measurement and prediction of radiological progression in early rheumatoid arthritis	Study design
Plant (2000)[261]	Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis	No measure of predictive performance reported
Posthumus (2000)[262]	Serum matrix metalloproteinase 3 in early rheumatoid arthritis is correlated with disease activity and radiological progression	Study design
Putrik (2016)[263]	Less educated and older patients have reduced access to biologic DMARDs even in a country with highly developed social welfare (Norway): results from Norwegian cohort study NOR-DMARD	Not an eligible end point
Quinn (2003)[264]	Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol	Not early RA
Quinn (2006)[265]	Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome	Limited reporting of predictive performance
Rech (2016)[266]	Prediction of disease relapses by multibiomarker disease activity and autoantibody status in patients with rheumatoid arthritis on tapering DMARD treatment	Not early RA
Rezaei (2012)[267]	In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial	Study design

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Rhodes (2010)[268]	A genetic association study of serum acute-phase C-reactive protein levels in rheumatoid arthritis: implications for clinical interpretation	Study design
Saevarsdottir (2011)[269]	Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial	No measure of predictive performance reported
Saevarsdottir (2011)[270]	Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts	No measure of predictive performance reported
Salaffi (2009)[271]	A predictive algorithm combining routine assessment and power Doppler ultrasonography for the development of rheumatoid arthritis from an early-onset undifferentiated arthritis	Not early RA
Scherer (2011)[272]	Distinct ACPA fine specificities, formed under the influence of HLA shared epitope alleles, have no effect on radiographic joint damage in rheumatoid arthritis	Study design
Scott (2000)[273]	Prognostic factors in early rheumatoid arthritis	Review
Scott (2013)[274]	Prediction model for rheumatoid arthritis: modelling 46 genetic risk variants with smoking	Study design
Semb (2014)[275]	Development of a transatlantic cardiovascular risk calculator for rheumatoid arthritis (ATACC-RA)	Study design
Semb (2015)[276]	Development of a transatlantic cardiovascular risk calculator for rheumatoid arthritis	Study design
Shen (2010)[277]	Serum biomarkers predict progressive structural damage in the BeSt study	Limited reporting of methods/results
Shen (2015)[278]	Sparse kernel machine regression for ordinal outcomes	No measure of predictive performance reported
Sjoblom (1984)[279]	Factors related to the progression and joint destruction in rheumatoid arthritis	Not early RA
Smolen (2006)[100]	Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial	Study design
Smolen (2013)[280]	Forget personalised medicine and focus on abating disease activity	Commentary
Solomon (2015)[281]	Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study	Not eligible outcome

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Sparks (2013)[282]	Performance of prediction models for rheumatoid arthritis serological phenotypes among women using family history, genetics and environmental factors	Modelling risk of RA
Stucki (1997)[283]	Management of rheumatoid arthritis	Literature review
Suarez-Almazor (1994)[284]	Outcome in rheumatoid arthritis. A 1985 inception cohort	Study design
Syversen (2010)[285]	Prediction of radiographic progression in rheumatoid arthritis and the role of antibodies against mutated citrullinated vimentin: results from a 10-year prospective study	No measure of predictive performance reported
Tchetverikov (2003)[286]	Matrix metalloproteinases-3, -8, -9 as markers of disease activity and joint damage progression in early rheumatoid arthritis	No measure of predictive performance reported
Teitsson (1984)[287]	Prospective study of early rheumatoid arthritis. I. Prognostic value of IgA rheumatoid factor	No measure of predictive performance reported
Ting (2008)[288]	Development of a health care utilisation data-based index for rheumatoid arthritis severity: a preliminary study	Duration of symptoms at baseline not reported. Not an eligible outcome
Tobón (2013)[289]	First-year radiographic progression as a predictor of further progression in early arthritis: results of a large national French cohort	$\leq$ 80% of the study population had RA and no early RA subgroup available
Uhlig (2000)[290]	The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up	Does not meet early RA definition
van Beers-Tas (2015)[291]	How does established rheumatoid arthritis develop, and are there possibilities for prevention?	Literature review
van den Broek (2013)[292]	The clinical relevance of rapid radiological progression in the first year of treatment during 8 years of follow-up of early rheumatoid arthritis patients	Conference abstract. Appears to be linked with van den Broek *et al.*[293]
van den Broek (2012)[293]	Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up	Study design
van der Heijde (1992)[294]	Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients	Limited reporting of predictive performance
van der Heide (1995)[295]	Prediction of progression of radiological damage in newly diagnosed rheumatoid arthritis	Limited reporting of predictive performance
van der Helm-van Mil (2005)[296]	Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis	Study design
van der Helm-van Mil (2008)[297]	Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving towards individualised treatment decision-making	Not early RA

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
van der Helm-van Mil (2010)[298]	Genetic variants in the prediction of rheumatoid arthritis	Modelling risk of RA
van der Helm-van Mil (2013)[299]	An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression	Measure of predictive performance not appropriate to review question
van Jaarsveld (1999)[300]	The prognostic value of the antiperinuclear factor, anti-citrullinated peptide antibodies and rheumatoid factor in early rheumatoid arthritis	Limited reporting of predictive performance
van Nies (2015)[301]	Evaluating processes underlying the predictive value of baseline erosions for future radiological damage in early rheumatoid arthritis	No measure of predictive performance
van Steenbergen (2013)[302]	Anaemia to predict radiographic progression in rheumatoid arthritis	No measure of predictive performance reported
van Zeben (1991)[303]	Association of HLA-DR4 with a more progressive disease course in patients with rheumatoid arthritis	Study design
van Zeben (1993)[304]	Factors predicting outcome of rheumatoid arthritis: results of a follow up study	Symptom duration at baseline unclear
Varache (2011)[305]	Diagnostic accuracy of ACR/EULAR 2010 criteria for rheumatoid arthritis in a 2-year cohort	Study design
Vastesaeger (2008)[94]	Matrix risk model for prediction of rapid radiographic progression in rheumatoid arthritis	Preliminary report of included study. No further relevant data reported
Versteegh (2010)[306]	Mapping onto Eq-5 D for patients in poor health	Study design
Vesperini (2013)[307]	Association of tobacco exposure and reduction of radiographic progression in early rheumatoid arthritis: results from a French multicentre cohort	No measure of predictive performance reported
Visser 2002[308]	How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis	Study design. Mixed early arthritis population
Visser (2009)[309]	The BeSt matrix model in recent-onset rheumatoid arthritis patients: individual prediction of rapid radiographic progression and numbers-needed-to-treat with initial combination therapy	Preliminary report of included study. No further relevant data reported
Visser (2009)[310]	The clinical relevance of a prediction rule for disease outcome in patients with undifferentiated arthritis: comment on the article by van der Helm-van Mil *et al.*	Letter to editor
Visvanathan (2007)[311]	Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis	No measure of predictive performance reported

continued

TABLE 21 Review 1 excluded full-text studies with rationale (*continued*)

First author (date of publication)	Title of publication	Justification for exclusion
Wessels (2007)[312]	A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis	Not an eligible outcome. DAS not DAS28 (borderline exclusion)
Westedt (1986)[313]	Serum immune complexes containing IgA appear to predict erosive arthritis in a longitudinal study in rheumatoid arthritis	No measure of predictive performance reported
Weyand (1992)[314]	The influence of *HLA-DRB1* genes on disease severity in rheumatoid arthritis	Not early RA
Widdifield (2013)[315]	Accuracy of Canadian health administrative databases in identifying patients with rheumatoid arthritis: a validation study using the medical records of rheumatologists	Study design
Wolfe (1998)[316]	Radiographic outcome of recent-onset RA: a 19-year study of radiographic progression	Limited reporting of predictive performance
Wolfe (2000)[317]	A reappraisal of HAQ disability in rheumatoid arthritis	Study design. No measure of predictive performance reported
Wolfe (2000)[318]	The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis	Not early RA
Wong (2004)[319]	Development and evaluation of a patient self-report case-finding method for rheumatoid arthritis	Study design
Yamanaka (2000)[320]	Serum matrix metalloproteinase 3 as a predictor of the degree of joint destruction during the six months after measurement, in patients with early rheumatoid arthritis	Study design. No measure of predictive performance reported
Young (1987)[321]	A prospective study of early onset rheumatoid arthritis over fifteen years: prognostic features and outcome	Limited reporting of predictive performance
Young (1988)[322]	A prognostic index for erosive changes in the hands, feet and cervical spines in early rheumatoid arthritis	Limited reporting of predictive performance
Young (1997)[323]	Can we predict aggressive disease?	Review
Young (2000)[324]	Socioeconomic deprivation and rheumatoid disease: what lessons for the health service?	No measure of predictive performance reported
Young-Min (2007)[325]	Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers	No eligible factor included in baseline model for radiographic progression. Longitudinal model time frame outside 2-year early RA definition

Appendix 5 Additional calculations for data extractions

Obtaining estimates of logit(C) and standard error

External validation studies that reported the *c*-statistic were considered. The logit transform is used to put the reported value on a suitable scale for analysis. Granger *et al.*[82] and Heimans *et al.*[84] report the associated CIs that can be used to obtain the standard error as follows:

$$\left\{[logit(C_{ub}) - logit(C_{lb})] / (2 \times 1.96)^2\right\}^2. \quad (14)$$

No appropriate estimates of uncertainty are provided in the De Cock *et al.*[80] validation, but the standard error was approximated from the total number of observed events, expected events and the sample size, as described in Debray *et al.*[40] (*Appendix 6*):

$$Var(logit(C)) \approx \frac{1 + \frac{s^*(1-c)}{2-c} + \frac{s^*c}{1+c}}{O(N-O)c(1-c)}, \quad (15)$$

in which O is the total number of observed events, N is the total sample size and:

$$s^* = \frac{N}{2} - 1. \quad (16)$$

Calculating the expected number of events

When possible, the expected number of events was calculated for each risk model evaluated in each external validation population. Here, we give an example of calculating the number of expected events for one risk model only, the Syversen model,[76] chosen as it has a smaller number of risk categories than other externally validated risk models.

For each risk category, the PR is provided in the published risk development study. The number of individuals in the external validation study who are assigned to each risk category (N) is provided in the external validation study (De Cock *et al.*[80] in this example). The expected number of events in each risk category (E) is computed by multiplying the PR and the number of individuals. The total number of expected events is then found by summing these expected numbers over all risk categories (*Table 22*).

Calculating distribution of linear predictor (case mix)

For each risk category, the PR is provided in the published risk development study and the number of individuals in the external validation study who are assigned to each risk category (N) is provided in the external validation study. These can be used to work out the distribution of risks (*Figures 8* and *9*).

TABLE 22 Calculation of expected number of events for the Syversen risk model in the De Cock *et al.*[80] external validation population

		De Cock *et al.*[80] population		
Risk category	PR	N	E	O
1	0.0928	0	0	0
2	0.2535	1	0.2535	0
3	0.2891	0	0	0
4	0.5744	2	1.1488	1
5	0.2460	5	1.23	1
6	0.5200	5	2.6	0
7	0.5646	3	1.6938	0
8	0.8115	5	4.0575	0
9	0.2387	1	0.2387	0
10	0.5100	4	2.04	1
11	0.5548	6	3.3288	0
12	0.8053	9	7.2477	0
13	0.5000	1	0.5	0
14	0.7685	4	3.074	0
15	0.7990	10	7.99	1
16	0.9296	17	15.8032	
Total		73	51.206	4

E, expected number of events; N, number of events; O, total number of observed events.
Note
O : E is 0.078.

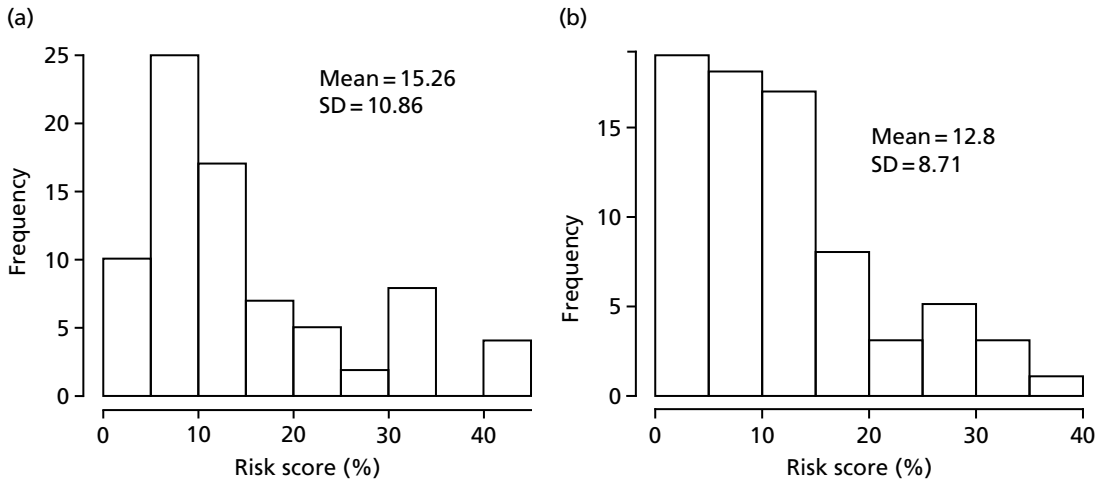

FIGURE 8 Distribution of linear predictor (case mix) for risk models in the De Cock *et al.*[80] external validation population. (a) ASPIRE CRP; (b) ASPIRE ESR; (c) BeSt; (d) ESPOIR; (e) SWEFOT 2; and (f) Syversen. (*continued*)

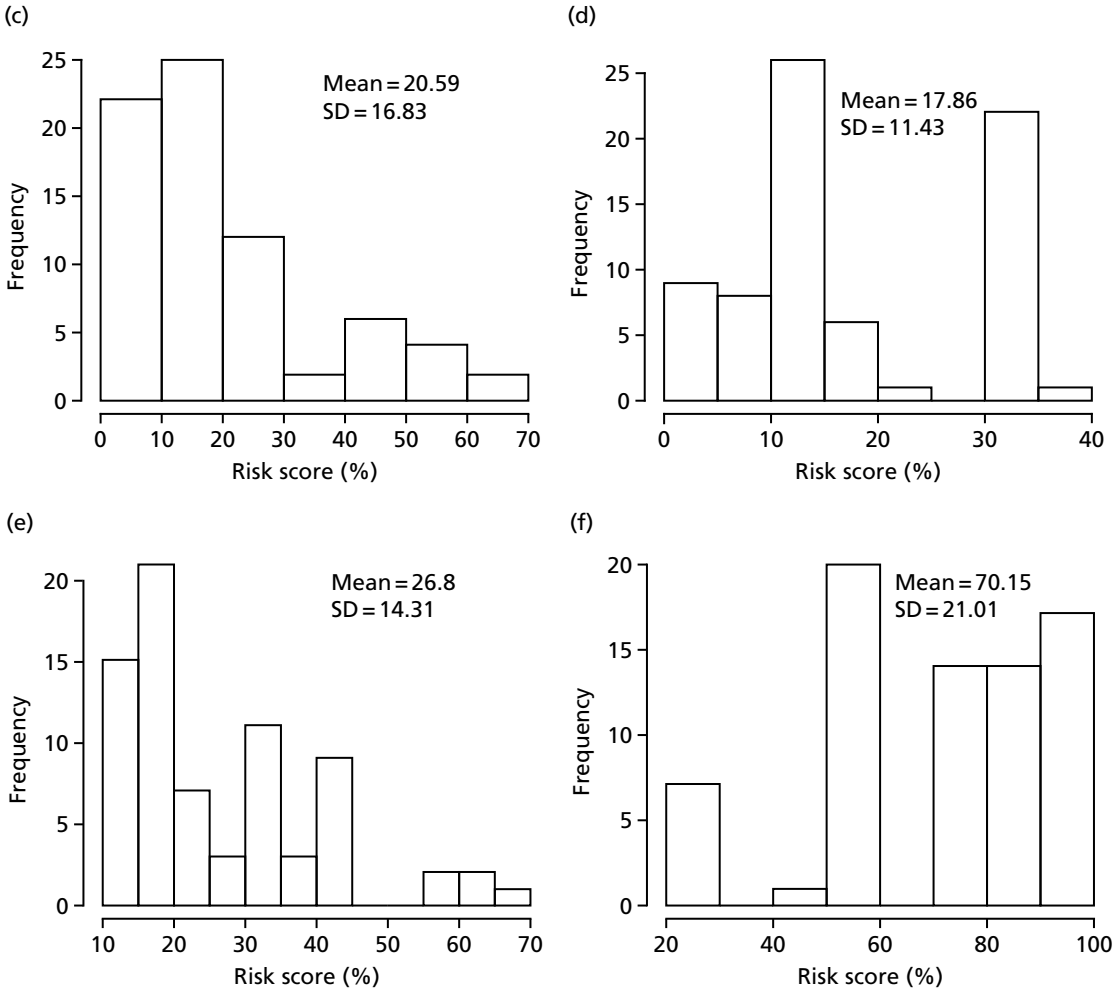

FIGURE 8 Distribution of linear predictor (case mix) for risk models in the De Cock *et al.*[80] external validation population. (a) ASPIRE CRP; (b) ASPIRE ESR; (c) BeSt; (d) ESPOIR; (e) SWEFOT 2; and (f) Syversen.

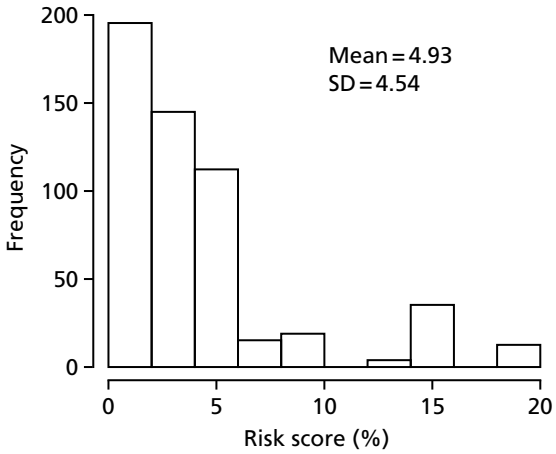

FIGURE 9 Distribution of linear predictor (case mix) for the BeSt models in Heimans *et al.*[84] external validation population.

Calculating risk probabilities for the Syversen model

The final risk model provided in Syversen *et al.*[76] is given as:

$$log\left(\frac{p}{1-p}\right) = -2.28 + 1.38I_{antiCCP+ve} + 1.20 \times I_{female} + 1.16 \times I_{highESR} + 1.12 \times I_{RF+ve}. \quad (17)$$

This results in the following risk matrix, which provides the risks for each combination of factors (*Table 23*).

TABLE 23 Risk matrix for Syversen *et al.*[76]

		ACPA status			
		ACPA–		ACPA+	
RF status	ESR	Male	Female	Male	Female
RF positive	High	0.5	0.7685	0.799	0.9296
	Low	0.2387	0.51	0.5548	0.8053
RF negative	High	0.246	0.52	0.5646	0.8115
	Low	0.0928	0.2535	0.2891	0.5744

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.
Note
Blue, 90%; light green, 80%; light blue, 50%; dark green, 20%; dark blue, 10%.

Appendix 6 Quality assessment results for Prediction model study Risk Of Bias Assessment Tool domains 1, 2 and 3 (review 1)

Prediction model study Risk Of Bias Assessment Tool domain 1: participant selection

TABLE 24 Domain 1A: risk of bias (prediction model development studies)

Name of risk model	Were appropriate data sources used?	Were all inclusions and exclusions of participants appropriate?	Risk of bias introduced by the selection of participants
ASPIRE[78]	Y	Y	Low
Bansback[58]	Y	Y	Low
Berglin[59]	Y	Y	Low
BeSt[79]	Y	Y	Low
Brennan[60]	Y	Y	Low
Centola[61]	Y	Y	Low
Combe (A)[62]	Y	Y	Low
Combe (B)[63]	Y	Y	Low
de Punder[64]	Y	Y	Low
de Vries-Bouwstra[65]	Y	Y	Low
Degboé[66]	Y	Y	Low
Dirven[67]	Y	Y	Low
Dixey[68]	Y	Y	Low
Drossaers-Bakker[56]	Y	PY[a,b]	Unclear
ESPOIR[69]	Y	Y	Low
Forslind[70]	Y	Y	Low
Graell[71]	Y	Y	Low
Houseman[72]	Y	Y	Low
Sanmartí[75]	Y	Y	Low
SONORA[57]	Y	NI[b]	Unclear
SWEFOT[73]	Y	Y	Low
Syversen[76]	Y	PY[c]	Unclear
van Steenbergen[77]	Y	Y	Low

NI, no information; PY, probably yes; Y, yes.
a Females only recruited.
b Method of RA diagnosis is unclear.
c Permitted disease duration up to 4 years.

Prediction model study Risk Of Bias Assessment Tool domain 1: participant selection

TABLE 25 Domain 1A: risk of bias (external validation studies)

First author of external validation study	Were appropriate data sources used?	Were all inclusions and exclusions of participants appropriate?	Risk of bias introduced by the selection of participants
De Cock[80]	Y	PY[a]	Unclear
Granger[82]	Y	Y	Low
Hambardzumyan[83]	Y	Y	Low
Heimans[84]	Y	PY[b]	Unclear
Markusse[85]	Y	Y	Low

PY, probably yes; Y, yes.
a Method of RA diagnosis is unclear.
b *c*-Statistic was apparently reported for a mixed RA/undifferentiated arthritis population. Therefore, the data in this trial relate to a mixed early arthritis population.

TABLE 26 Domain 2A: risk of bias (prediction model development studies)

Name of risk model	Were predictors defined and assessed in a similar way for all participants?[a]	Were predictor assessments made without knowledge of outcome data?[b]	Were all (*final*) predictors available at the time at which the model was intended to be used?	Were all relevant predictors analysed (i.e. all selected prognostic factors analysed as candidate predictors)?	Risk of bias introduced by predictors or their assessment (low/high/unclear)[c]
ASPIRE[78]	PY	Y	Y	No ACPA status, DAS28, smoking status, HAQ score or early RA untreated for ≥ 12 weeks following the onset of symptoms	Unclear
Bansback[58]	PY	Y	PY (dependent on availability of the Carstairs index)	No ACPA status, CRP levels or smoking status	Unclear
Berglin[59]	PY	Y	Y	No early RA untreated for ≥ 12 weeks following the onset of symptoms, HAQ score or smoking status	Unclear
BeSt[79]	PY	Y	Y	No DAS28 (DAS only)	Low
Brennan[60]	PY	Y	Y	No ACPA status, erosions/joint damage on radiographic analysis, smoking status, ESR or DAS28	Unclear
Centola[61]	PY	PY	PY [dependent on the availability of biomarker assay(s)]	Biomarker tests only	Unclear[d]
Combe (A)[62]	PY	Y	PY (dependent on the availability of SE testing)	No ACPA status, DAS28 or smoking status	Unclear
Combe (B)[63]	PY	Y	Y	No ACPA status, DAS28 or smoking status	Unclear
de Punder[64]	PY	Y	Y	No early RA untreated for ≥ 12 weeks following the onset of symptoms or HAQ score	Unclear
de Vries-Bouwstra[65]	PY	Y	PY (dependent on the availability of SE testing)	No ACPA status, CRP levels, DAS28 or smoking status	Unclear

continued

DOI: 10.3310/hta22660

TABLE 26 Domain 2A: risk of bias (prediction model development studies) (*continued*)

Name of risk model	Were predictors defined and assessed in a similar way for all participants?[a]	Were predictor assessments made without knowledge of outcome data?[b]	Were all (*final*) predictors available at the time at which the model was intended to be used?	Were all relevant predictors analysed (i.e. all selected prognostic factors analysed as candidate predictors)?	Risk of bias introduced by predictors or their assessment (low/high/unclear)[c]
Degboé[66]	PY	Y	PY (dependent on the availability of anti-MCV, AhFibA testing)	No SJC, ESR, DAS28, smoking status or HAQ score	Unclear
Dirven[67]	PY	Y	Y	No DAS28 (DAS only)	Low
Dixey[68]	PY	Y	Y	No ACPA status, CRP levels, DAS28 or smoking status	Unclear
Drossaers-Bakker[56]	PY	Y	PY (alternative models provided with available predictors)	No ACPA status, CRP levels, DAS28 or smoking status	Unclear
ESPOIR[69]	PY	Y	Y	No smoking status	Low
Forslind[70]	PY	Y	Y	No SJC, smoking status or early RA untreated for ≥ 12 weeks following the onset of symptoms	Unclear
Graell[71]	PY	Y	Y	No smoking status	Low
Houseman[72]	PY	PY (anti-CCP measured at 8.2 years)	PY (dependent on the availability of MMP-3 testing)	No SJC, DAS28, smoking status, HAQ score or early RA untreated for ≥ 12 weeks following the onset of symptoms	Unclear
Sanmartí[75]	PY	Y	PY (dependent on the availability of HLA-DRB1*04 test)	Assumed same as for Graell *et al.*[71] and, therefore, no smoking status	Low
SONORA[57]	NI	Y	Y	NI	Unclear

Name of risk model	Were predictors defined and assessed in a similar way for all participants?[a]	Were predictor assessments made without knowledge of outcome data?[b]	Were all (*final*) predictors available at the time at which the model was intended to be used?	Were all relevant predictors analysed (i.e. all selected prognostic factors analysed as candidate predictors)?	Risk of bias introduced by predictors or their assessment (low/high/unclear)[c]
SWEFOT[73]	PY	Y	Y	Y	Low
Syversen[76]	PY	Y	Y	No SJC, DAS28, smoking status or early RA untreated for ≥ 12 weeks following the onset of symptoms	Unclear
van Steenbergen[77]	PY	Y	PY (dependent on the availability of genetic tests)	No erosions at baseline, CRP levels, DAS28, smoking status or HAQ score	Unclear

NI, no information; PY, probably yes; Y, yes.
a If not reported (but there was no evidence to the contrary), it was rated as 'probably yes'.
b If the predictors measured at baseline and the outcomes at a subsequent time point were rated as 'yes'.
c Rated as being unclear if two or more key candidate predictors of interest were not assessed (as the potential contribution of untested predictors to the final model is unknown).
d Although the study design focused on the inclusion of biomarkers only, the potential contribution of other characteristics of interest to the final model is unclear.

TABLE 27 Domain 2A: risk of bias (external validation studies)

First author of external validation study	Were predictors defined and assessed in a similar way for all participants?[a]	Were predictor assessments made without knowledge of the outcome data?[b]	Risk of bias introduced by predictors or their assessment (low/high/unclear)
De Cock[80]	PY	Y	Low
Granger[82]	PY	Y	Low
Hambardzumyan[83]	PY	Y	Low
Heimans[84]	PY	Y	Low
Markusse[85]	PY	Y	Low

PY, probably yes; Y, yes.
a If this is not reported, but there is no evidence to the contrary, then it is rated as 'probably yes'.
b If the predictors measured at baseline and the outcomes at a subsequent time point are rated as 'yes'.

Prediction model study Risk Of Bias Assessment Tool domain 3: outcomes

TABLE 28 Domain 3A: risk of bias (prediction model development studies)

Name of risk model	Was a prespecified outcome definition used?[a]	Was the outcome defined and determined in a similar way for all participants?[b]	Was the outcome determined without knowledge of predictor information?	Risk of bias introduced by outcome or its determination (low/high/unclear)
ASPIRE[78]	Y	PY	PY	Low
Bansback[58]	PY	PY	NI	Unclear
Berglin[59]	PY	PY	Y	Low
BeSt[79]	Y	PY	PY	Low
Brennan[60]	PY	PY	NI	Unclear
Centola[61]	PY	PY	NI	Unclear
Combe (A)[62]	Y	PY	Y	Low
Combe (B)[63]	PY	PY	NI	Unclear
de Punder[64]	Y	PY	NI	Unclear
de Vries-Bouwstra[65]	PY	PY	Y	Low
Degboé[66]	PY	PY	Y	Low
Dirven[67]	Y	PY	PY	Low
Dixey[68]	PY	PY	NI	Unclear
Drossaers-Bakker[56]	PY	PY	NI	Unclear
ESPOIR[69]	Y	PY	Y	Low
Forslind[70]	PY	PY	Y	Low
Graell[71]	PY	PY	NI	Unclear
Houseman[72]	PY	PY	PY	Low
Sanmartí[75]	Y	PY	NI	Unclear

TABLE 28 Domain 3A: risk of bias (prediction model development studies) (*continued*)

Name of risk model	Was a prespecified outcome definition used?[a]	Was the outcome defined and determined in a similar way for all participants?[b]	Was the outcome determined without knowledge of predictor information?	Risk of bias introduced by outcome or its determination (low/high/unclear)
SONORA[57]	PY	PY	NI	Unclear
SWEFOT[73]	Y	PY	NI	Unclear
Syversen[76]	PY	PY	Y	Low
van Steenbergen[77]	PY	PY	Y	Low

NI, no information; PY, probably yes; Y, yes.
a If a clear justification is given for the definition of the outcome, it is rated as 'yes'. If it is not reported, but there is no evidence to the contrary, it is rated as 'probably yes'.
b If it is not reported, but there is no evidence to the contrary, it is rated as 'probably yes'.

TABLE 29 Domain 3A: risk of bias (external validation studies)

Name of external validation study	Was a prespecified outcome definition used?[a]	Was the outcome defined and determined in a similar way for all participants?[b]	Was the outcome determined without knowledge of predictor information?	Risk of bias introduced by outcome or its determination (low/high/unclear)
De Cock[80]	Y	PY	NI	Unclear
Granger[82]	Y	PY	Y (blinded to clinical evaluation)	Low
Hambardzumyan[83]	Y	PY	NI	Unclear
Heimans[84]	Y	PY	PY (blinded to patient identity)	Low[c]
Markusse[85]	PY	PY	PY (blinded to patient identity)	Low

NI, no information; PY, probably yes; Y, yes.
a If a clear justification is given for the definition of the outcome, it is rated as 'yes'. If it is not reported, but there is no evidence to the contrary, it is rated as 'probably yes'.
b If it is not reported, but there is no evidence to the contrary, it is rated as 'probably yes'.
c Note that the predicted outcome applied in the external validation differed from that in the original model development paper.

Appendix 7 Additional evidence tables: review 1

TABLE 30 Additional baseline population characteristics of the included risk prediction model development and external validation studies

Name of risk model/external validation study (number of baseline characteristics reported)	Characteristic				
	Age	Sex	HAQ score	Radiographic joint damage	ACPA/anti-CCP status
Risk model development studies					
ASPIRE[78] ($n = 1049$)	Median age: 51 years (IQR 41–60 years)	71.1% female	Median (scale 0–3): 1.5 (IQR 1.0–1.9)	Median total modified SHS: 5.0 (IQR 1.5–14.0) 82% ($n = 854$) of patients with joint erosion 65.9% ($n = 687$) of patients with JSN 0.3% of patients ($n = 3$) with prior joint surgery	NR
Bansback[58] ($n = 985$, NR across total sample)	Aged 17–93 years at disease onset (median 55 years, IQR NR)	Female: $n = 654$ (66%)	Median: 1.00 (IQR NR)	$n = 241$ (24%) had erosions at baseline	NR
Berglin[59]	NR [mean age at onset of symptoms was 54 years (range 23–73 years)]	NR	NR	NR	Anti-CCP: 74.8%
BeSt[79] (Reported for 465/508; NR for whole sample, reported by treatment group)	Mean age: 54 years across groups (SD 13–14 years)	Female sex: 66–70% across groups (SD 66–70%)	HAQ score of 1.4 across groups (0.6 to 0.7)	Median erosions: 1.8–2.0 across groups (IQR 0.5–4.5) Total median SHS: 3.3–4.0 across groups (IQR 1.5–8.5)	ACPA+: 55–64%
Brennan[60] (Total population, $n = 175$)	18–51 years: 32% 52–66 years: 34% > 66 years: 34%	71% female	HAQ score ≥ 1 (scale 0–3): 59%	NR	NR
Centola[61] (Feasibility studies I–IV, $n = 652$; algorithm training study stage 3, $n = 249$ samples)	Feasibility studies I–IV (stage 2), mean age: 59 years Algorithm training study (stage 3), median age: 58 years (IQR 49–67 years)	Feasibility studies I–IV (stage 2): 77–91% female Algorithm training study (stage 3): 75% female	Feasibility studies I–IV (stage 2): NR Algorithm training study (stage 3): NR	Feasibility studies I–IV (stage 2): NR Algorithm training study (stage 3): NR	Feasibility studies I–IV (stage 2): 61–63% CCP positive Algorithm training study (stage 3): 58% anti-CCP positive
Combe A[62] ($n = 191$)	Mean age at diagnosis: 50.5 years (SD 14.7 years)	73.3% female	Mean: 1.3 (SD 0.7)	Mean Sharp score: 3.6 (SD 7.7)	NR
Combe B[63] ($n = 191$)	Mean age: 50.5 years (SD 14.7 years)	73% female	NR Mean: 1.3 (range 0–2.75)	NR Erosion score, mean: 1.7 (range 0–33.0)	NR
de Punder[64] ($n = 425$; NR for total group)	Mean age: • Joint damage progressors: 54 years (SD 14 years) • Non-progressors: 57 years (SD 14 years)	Joint damage progressors: 59% Non-progressors: 66%	NR	Erosions: • Joint damage progressors: 62% • Non-progressors: 32%	Anti-CCP positive: • Joint damage progressors: 82% • Non-progressors mean: 53%
de Vries-Bouwstra[65] ($n = 152$)	Median age: 66 years (IQR 55–76 years)	68% female	NR	Patients with erosions in hands or feet: 57 (38%)	NR
Degboé[66] ($n = 566$)	Median age: 50.5 years (IQR 40.2–57.0 years)	78.6% female	NR	mTSS, median: 3 (IQR 0–7)	ACPA+: 333

RF status	SJC	TJC	ESR	CRP level	Smoking status
Median: = 175 U/ml (IQR 30–357 U/ml)	Median: 19 (IQR 14–26)	Median: 31 (IQR 22–44)	Median: 40 mm/hour (IQR 23–61 mm/hour)	Median:1.4 mg/dl (IQR 0.4–4.1 mg/dl)	NR
74% ($n = 730$) of patients were seropositive at baseline	NR	NR	NR	NR	NR
IgM RF: 85.7% IgA RF: 78.6% IgG RF: 46.8%	NR	NR	NR	NR	NR
RF positive: 62.66%	Median: 13–14 across groups	Median: 11–14	Median: 35–38 mm/hour across groups	Median: 21–22 mg/l across groups	NR
NR	NR	NR	NR	NR	NR
Feasibility studies I–IV (stage 2): 64–97% positive Algorithm training study (stage 3): 61% positive	Feasibility studies I–IV (stage 2), median SJC28: 2.0 (IQR 0.0–10) to 16 (IQR 12–21) Algorithm training study (stage 3), median: 4 (IQR 0–17)	Feasibility studies I–IV (stage 2), median TJC28: 2.0 (IQR 0–8.3) to 12 (IQR 4.8–20) Algorithm training study (stage 3), median: 5 (IQR 0–18)	Feasibility studies I–IV (stage 2): NR Algorithm training study (stage 3): NR	Feasibility studies I–IV (stage 2), median: 14 mg/l (IQR 4.0–32 mg/l) to 18 mg/l (IQR 6.9–47 mg/l) Algorithm training study (stage 3), median: 3.8 mg/l (IQR 1.3–20.5 mg/l)	Feasibility studies I–IV (stage 2): NR Algorithm training study (stage 3): NR
RF positive: 80.6% IgM RF: 68.0% IgA RF: 75.4%	Mean: 9 (SD 5.9)	Mean: 21 (SD 10)	Mean: 40.2 mm/hour (SD 28.5 mm/hour)	Mean: 34.1 mg/l (SD 43.2 mg/l)	NR
IgA or IgM RF positive: 80.8%	Mean: 9.0 (SD 5.9)	Mean: 21.7 (SD 10.5)	Mean: 40.2 mm/hour (SD 28.5 mm/hour)	Mean: 34.1 mg/l (SD 43.2mg/l)	NR
RF positive: • Joint damage progressors: 87% • Non-progressors: 66%	SJC28: • Joint damage progressors, median: 11 (IQR 7–16) • Non-progressors, median: 10 (IQR 6–14)	TJC28: Joint damage progressors, median: 7 (IQR4–13) Non-progressors, median: 6 (IQR 2–12)	Joint damage progressors, median: 40 mm/hour (IQR 21–59 mm/hour) Non-progressors, median: 21 mm/hour (IQR 9–38 mm/hour)	Joint damage progressors, median: 22 mg/l (IQR 7–52 mg/l) Non-progressors, median: 3 mg/l (IQR 0–23 mg/l)	Smoker status (ever): • Joint damage progressors: 72% • Non-progressors: 67%
IgM RF positive: 93 (61%)	Median number swollen joints: 6 (IQR 4–8)	NR	NR	NR	NR
RF positive: 54.2%	NR	NR	Median: 22 mm/hour (IQR 12–37 mm/hour)	Median: 9 mg/l (IQR 0–21 mg/l)	Smokers: 48.1%

TABLE 30 Additional baseline population characteristics of the included risk prediction model development and external validation studies (*continued*)

Name of risk model/external validation study (number of baseline characteristics reported)	Characteristic				
	Age	Sex	HAQ score	Radiographic joint damage	ACPA/anti-CCP status
Dirven[67] (NR for total group; MTX mono, $n = 239$; combination and prednisone, $n = 131$; combination and IFX, $n = 127$)	Mean age: • MTX monotherapy: 54 years (SD 13 years) • Combination and prednisone: 55 years (SD 14 years) • Combination and IFX: 54 years (SD 14 years)	MTX monotherapy: 70% Combination and prednisone: 66% Combination and IFX: 66%	Mean: 1.4 (SD 0.6–0.7) across groups	Median total SHS: • MTX monotherapy: 4.0 (IQR 1.5–8.8) • Combination and prednisone: 3.5 (IQR 1.5–8.5) • Combination and IFX: 4.0 (IQR 1.5–8.8) Erosive (≥ 1): • MTX monotherapy: 71% • Combination and prednisone: 71% • Combination and IFX: 73%	ACPA positive: • MTX monotherapy: 63% • Combination and prednisone: 55% • Combination and IFX: 66%
Dixey[68] ($n = 866$)	• Age at onset: < 45 years, 24% • 45–60 years, 40% • > 60 years, 36%	66% female	NR	Erosion score: • 0, 68% • 1, 11% • > 1, 21%	NR
Drossaers-Bakker[56] ($n = 112$)	Mean age: 37 years (SD 8.4 years)	100% female	Median: 0.75 (IQR NR) (range 0–2.88)	Median SHS: 12 (IQR NR) Presence of erosions: 22%	NR
ESPOIR[69] ($n = 370$)	Mean age: 49.4 years (SD 11.4 years)	73.2% female	Mean HAQ score: 1.03 (SD 0.7)	18% with typical RA erosion on radiographs Mean vSHS 6.02 (SD 9.7)	ACPA positivity: 50%
Forslind[70] ($n = 379$)	Median age: 55 years (IQR 45–67 years)	65% female	HAQ score (scale 0–3), median: 0.90 (IQR 0.50–1.38)	Larsen score scale range (0–200), median: 4 (IQR 0–10)	NR
Graell[71] ($n = 105$)	Mean age: 55 years (SD 14.9 years)	81% female	MHAQ, mean score: 0.97 (SD 0.56)	Larsen score, mean: 1.2 (SD 2.7)	Anti-CCP positive: 70.4%
Houseman[72] ($n = 58$)	Mean age: 53 years (SD 11 years)	64% female	Median: 1.4 (IQR 0.9–2.1)	Larsen score, median: 1 (IQR 0–2.5)	NR
Sanmartí[75] ($n = 105$)	Mean age: 55 years (SD 14.9 years)	81% female	MHAQ, mean score: 1 (SD 0.6)	Larsen score, mean: 1.2 (SD 2.7) Erosion joint count, mean: 0.4 (SD 0.9)	Anti-CCP positive: 70.4%
SONORA[57] ($n = 994$)	Mean age: 53 years (SD 14.81 years)	72% female	NR	Sharp score, mean: 5.49 (SD 7.85) ($n = 746$)	NR
SWEFOT[73] ($n = 269$)	Median age: 57 years (IQR 46–63 years)	28% male	HAQ score: 1.1 (IQR 0.9–1.6)	SHS, median: 2 (IQR 0–6) JSN score, median: 0 (IQR 0–3) Erosion score, median: 0 (IQR 0–2), 42% erosions	Anti-CCP positive: 62%
Syversen[76] ($n = 238$)	Mean age: 51.9 years (SD 13.0 years)	73.5% female	Mean: 0.9 (SD 0.6)	Erosive disease: 55.2%	Anti-CCP positive: 60.5%
van Steenbergen[77] ($n = 426$)	Mean age : 56.6 years (SD 15.3 years)	68.1% female	NR	SHS, median: 5.0 (IQR 2.0–10.0)	ACPA+: 53.3%

RF status	SJC	TJC	ESR	CRP level	Smoking status
RF positive: • MTX monotherapy: 65% • Combination and prednisone: 65% • Combination and IFX: 64%	• Median: MTX monotherapy: 14 (IQR 10–20) • Combination and prednisone: 14 (IQR 10–18) • Combination and IFX: 13 (IQR 9–17)	Median: • MTX monotherapy: 22 (IQR 14–31) • Combination and prednisone: 22 (IQR 13–33) • Combination and IFX: 19 (IQR 12–22)	Median: • MTX monotherapy: 38 mm/hour (IQR 21–58 mm/hour) • Combination and prednisone: 35 mm/hour (IQR 17–45 mm/hour) • Combination and IFX: 36 mm/hour (IQR 19–58 mm/hour)	Median: • MTX monotherapy: 22 mg/l (9–59 mg/l) • Combination and prednisone: 21 mg/l (10–57 mg/l) • Combination and IFX: 21 mg/l (7–44 mg/l)	Smoking status (yes/no): • MTX monotherapy: 39% • Combination and prednisone: 34% • Combination and IFX: 32%
RF negative: 27%	NR	NR	NR	NR	NR
RF positive: 55%	Median: 3.5 (IQR NR)	NR	Median: 27 mm/hour (IQR NR)	NR	NR
IgM RF positivity: 55.1%	Mean SJC28: 7.9 (SD 5.4)	Mean TJC28: 8.7 (SD 6.9)	Mean ESR: 32.7 mm/first hour (SD 25 mm/first hour)	Mean CRP level: 24.8 mg/l (SD 37.7 mg/l)	NR
RF positive: 61%	NR	NR	Median: 29 mm/hour (IQR 14–50 mm/hour)	Median: 19 mg/l (IQR 6–43 mg/l)	Current/previous smoker: 60%
RF positive: 73.3%	SJC28, mean: 8.3 (SD 4.1)	TJC28, mean: 10.1 (SD 5.9)	Mean: 39.5 mm/hour (SD 24.5 mm/hour)	Mean: 2.8 mg/dl (SD 2.9 mg/dl)	NR
RF positive: 77%	Median: 9 (IQR 4–14)	Median: 15 (IQR 6–18)	Median: 28 mm/hour (IQR 14–45 mm/hour)	Median: 17 mg/l (IQR 5–40 mg/l)	NR
RF positive: 74.3%	SJC28, mean: 8.3 (SD 4.1)	TJC28, mean: 10.1 (SD5.9)	Mean: 39.6 mm/hour (SD 24.5 mm/hour)	Mean: 2.8 mg/dl (SD 2.9 mg/dl)	NR
NR	NR	NR	NR	NR	NR
RF positive: 67% RF and ACPA+: 49%	SJC28, median: 10 (IQR 6–14)	TJC28, median: 8 (IQR 5–13)	Median: 34 mm/hour (IQR 22–54 mm/hour)	CRP level, median: 19 mg/l (IQR 9–47 mg/l)	Current smokers: 24% Past smokers: 37% Never smoked: 39%
IgA RF positive: 37.8% IgM RF positive: 47.9%	NR	NR	Median: 20.5 mm/hour (IQR 10.0–36.0 mm/hour)	Median: 5.3 mg/l (IQR 1.7–13.8 mg/l)	NR
IgM RF positive: 58.2%	SJC66, median: 8 (IQR 4–14)	NR	Median: 33.0 mm/hour (18.0–55.0 mm/hour)	NR	NR

continued

TABLE 30 Additional baseline population characteristics of the included risk prediction model development and external validation studies (*continued*)

Name of risk model/external validation study (number of baseline characteristics reported)	Characteristic				
	Age	Sex	HAQ score	Radiographic joint damage	ACPA/anti-CCP status
External validation studies					
De Cock[80] ($n = 74$)	Mean age: 52 years (SD 16 years)	65% female	Mean HAQ score (scale 0–3): 1.10 (SD 0.76)	NR	ACPA+: 71%
Granger[82] ($n = 370$)	Mean age: 49.4 years (SD 11.4 years)	73.2% female	Mean (HAQ score: 1.0 (SD 0.7)	Typical RA erosion: 17.8% vSHS baseline total score: 4.5 (SD 6.8)	ACPA+: 50%
Hambardzumyan[83] ($n = 487$)	NR	70% female	NR	Mean SHS: 4.5 (median 2)	Anti-CCP positive: 57%
Heimans[84] (RA $n = 479$)	Mean age: 52 years (SD 13 years)	70% female	NR	Median, total SHS: 0 (IQR 0–0) Erosive: 15%	ACPA+: 68%
Markusse[85] ($n = 508$)	NR for total group	NR for total group	NR for total group	NR for total group	NR for total group

ACPA+, anticitrullinated protein/peptide anti-body positive; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin; JSN, joint space narrowing; mTSS, total van der Heijde-modified Sharp score; NR, not reported; SJC66, 66 swollen joint count; TJC28, 28 tender joint count; vSHS, van der Heijde-modified Sharp score.

RF status	SJC	TJC	ESR	CRP level	Smoking status
RF positive: 71% RF: 224.7 U/ml (281.1 U/ml)	Total SJC, mean 12.45 (SD 8.19) SJC28, mean: 8.01 (SD 5.35)	Total TJC, mean: 14.35 (SD 10.59) TJC28, mean: 8.28 (SD 6.38)	Mean ESR: 36.66 mm/hour (SD 24.06 mm/hour)	Mean CRP level: 28.80 mg/l (33.78 mg/l)	Smokers: 28%
IgM RF positive: 55.1%	SJC, mean: 287.9 (SD 5.4)	TJC, mean: 288.7 (SD 6.9)	ESR, mean: 32.7 mm/first hour (SD 25 mm/first hour)	Mean CRP level: 24.8 mg/l (SD 37.7 mg/l)	NR
RF positive: 68%	SJC28, mean: 10.8 (SD 5.28)	TJC28, mean: 9.6 (SD 6.07)	Mean: 39.9 mm/hour (SD 25.9 mm/hour)	Mean: 33.8 mg/l (SD 36.81 mg/l)	NR
RF positive: 69%	Median SJC: 7 (IQR 3–11)	Median TJC: 7 (IQR 4–10)	NR	NR	NR
NR for total group	NR for total group	NR for total group	NR for total group	NR for total group	NR for total group

TABLE 31 Performance results from clinical prediction model development studies: additional performance measures

Name of clinical prediction model (*submodels*)	Other performance measures (e.g. sensitivity, specificity, PPV, NPV, accuracy)
Models predicting radiographic joint damage	
ASPIRE[78]	NR
ESR	
CRP	
Berglin[59]	Model 1: accuracy 73%
	Model 2: accuracy 67%
BeSt[79]	PPV and NPV reported for a range of PRs. At 60% PR (100% patients classified), PPV = 75% and NPV = 69%
ESR	
CRP	
Brennan[60]	Threshold of 0.5 PR
	Prediction sample: accuracy = 76/105 (72%)
	Validation sample: PPV = 76%; NPV = 80%; and accuracy = 79%
	Addition of second-line drugs and/or steroids tested: PPV = 72%; NPV = 82%; and accuracy = 79%
Combe (A)[62]	$p = 0.50$ as probability cut-off point
Two models	Model 1 (radiographic progression): sensitivity, 0.71; and specificity, 0.74
	Model 2 (high Sharp score of > 4): sensitivity, 0.78; and specificity, 0.85
de Punder[64]	NR
Extended	
Simplified	
de Vries-Bouwstra[65]	Presence of progression of radiological damage PPV = 75.3%
Degboé[66]	Anti-CCP2 (25 U/ml, 95% diagnosis specificity): PPV = 63.5%; and NPV, 57.5%
Four models	Anti-CCP2 (40 U/ml, 98% diagnosis specificity): PPV = 62.8%; and NPV, 58.4%
Anti-CCP	Anti-MCV (20 UA/ml, 95% diagnosis specificity): PPV = 64.8%; and NPV, 51.5%
Anti-MCV	Anti-MCV (35 UA/ml, 98% diagnosis specificity): PPV = 62.1%; and NPV, 57.5%
AhFibA	AhFibA (0.056 AU, 95% diagnosis specificity): PPV = 67.6%; and NPV, 53.4%[a]
High ACPA level	AhFibA (0.119 AU, 98% diagnosis specificity): PPV = 62.8%; and NPV, 56.3%[a]
Dixey[68]	Non-erosive group at baseline (68%): correctly predicted ERO or not by 3 years in 67% (sensitivity, 52%; specificity, 78%; and PPV, 68%). Severity of ERO predicted correctly in 82% (sensitivity, 96%; specificity, 42%; and PPV, 77%) and Larsen score and ESR at 1 year (90% correct; sensitivity, 98%; specificity, 52%; and PPV, 84%). Validity of each model tested in a random 40% subset of the cohort not used in the analysis and 'confirmed the prognostic value of these variables' (overall: 67.30% 79.20% and 87.20% in the test sample for the three models)
Three models	

TABLE 31 Performance results from clinical prediction model development studies: additional performance measures (*continued*)

Name of clinical prediction model (*submodels*)	Other performance measures (e.g. sensitivity, specificity, PPV, NPV, accuracy)
Drossaers-Bakker[56]	Mild radiographic damage: all (SJC, RF, ERO, SE), all-over correct, 88%; PPV, 80%; and NPV, 91% Selected (SJC, RF, ERO): all-over correct, 87%; PPV, 87%; and NPV, 86% Severe radiographic damage: all (SJC, RF, ERO, RAP), all-over correct, 85%; PPV, 91%; and NPV, 80% Selected (SJC, RF, ERO): all-over correct, 84%; PPV, 85%; and NPV, 74%
ESPOIR[69]	NR
Forslind[70]	Model 1 (radiological damage): accuracy, 78%; sensitivity, 0.79; specificity, 0.77; PPV, 0.79; and NPV, 0.77 Model 2 (radiological progression): accuracy, 75%; sensitivity, 0.75; specificity, 0.75; PPV, 0.77; and NPV, 0.73
Houseman[72]	Model for radiographic progression PPV = 81%, NPV = 85% Model for absolute radiographic outcome PPV = 87%, NPV 64%
Sanmartí[75]	Sensitivity, 53.9%; specificity, 81.7%; PPV, 56%; and NPV, 80.3%
SONORA[57]	NR
SWEFOT[73]	NR
Whole group	
Whole group stratified	
Anti-CCP	
Sex	
Syversen[76]	Model 1 (externally validated in De Cock *et al.*[80]): sensitivity, 89.2%; specificity, 51%; and accuracy, 73.6% Model 2 (adjusted for baseline radiographic score): sensitivity, 81.1%; specificity, 76.5%; and accuracy, 76.5% Model 3 (anti-CCP as a continuous variable): sensitivity, 86.5%; specificity, 64.7%; and accuracy, 77.6%
van Steenbergen[77]	NR
Models predicting HAQ/disease course	
Bansback[58]	NR
Combe (B)[63]	$p = 0.408$ (probability of 5-year HAQ score of > 1). PPV = 46.15%, NPV = 92.71%
Dirven[67]	67% patients reliably classified using cut-off points of < 35% (low risk) and > 60% (high risk); PPV = 71%; and NPV = 74%

continued

TABLE 31 Performance results from clinical prediction model development studies: additional performance measures (*continued*)

Name of clinical prediction model (*submodels*)	Other performance measures (e.g. sensitivity, specificity, PPV, NPV, accuracy)
Drossaers-Bakker[56]	Mild HAQ score: all (HAQ score, ERO), all-over correct, 88%; PPV, 89%; and NPV, 85%
	Selected (HAQ score, ERO), all-over correct, 88%; PPV, 89%; and NPV, 85%
	Severe HAQ score: all (HAQ score), all-over correct, 84%; PPV, 91%; and NPV, 72%
	Selected (HAQ score): all-over correct, 84%; PPV, 91%; and NPV, 72%
	Severe disease course: all (SJC, HAQ, SE), all-over correct, 80%; PPV, 84%; and NPV, 76%
	Selected (SJC, Ritchie score): all-over correct, 83%; PPV, 91%; and NPV, 76%
Graell[71]	Sensitivity, 70.1%; specificity, 64%; PPV, 83.9%; and NPV, 44.4%
Models predicting DAS28	
Centola[61]	NR

ERO, erosive; NR, not reported; RAP, rheumatoid arthritis protected; UA, undifferentiated arthritis.
a Original publication states AU without further details.

TABLE 32 Performance results from external validation studies – additional performance measures

Name of clinical prediction model (*submodels*)	Other performance measures (e.g. sensitivity, specificity, PPV, NPV, accuracy)
De Cock[80]	NR
Hambardzumyan[83]	Sensitivity, 0.98; specificity, 0.17; PPV = 0.21; and NPV = 0.97
Heimans[84]	RA (progression of ≥ 0.5 on the SHS, based on intermediate or higher risk for progression) PPV = 15.4%, NPV for no progression = 98.8%
Markusse[85]	NR

NR, not reported.

Appendix 8 Review 2 excluded studies

TABLE 33 Review 2 excluded studies with rationale

First author (date)	Title	Justification for exclusion
Addimanda (2014)[326]	Efficacy and safety of tocilizumab in refractory rheumatoid arthritis: a real life cohort from a single centre	Not early RA
Aga (2013)[327]	Clinical predictors of response to methotrexate treatment in DMARD naive patients with early rheumatoid arthritis: results from a longitudinal observational study	Treatment duration of < 6 months
Ajeganova (2013)[328]	Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset	Not prediction of treatment response
Akdemir (2014)[329]	Radiological outcomes after two years of remission steered treatment in early arthritis patients	Early RA and UA patients, results not separated
Akdemir (2014)[330]	ACPA-negative RA patients benefit from initial combination therapy with early clinical improvement-a sub-analysis of the best study	Not prediction of treatment response
Akdemir (2016)[331]	Predictive factors of radiological progression after two years of remission steered treatment in early arthritis patients	Early RA and UA patients, results not separated
Akhavan (2011)[122]	Prevalence of and predictive factors for sustained remission in early RA: Results from SONORA study	Not prediction of treatment response
Akhavan (2013)[332]	The impact of reaching low disease activity in the first year on future disability and damage in patients with early rheumatoid arthritis	Not prediction of treatment response
Akhavan (2014)[333]	Predictive validity of low disease activity using patient reported measures on long-term outcomes in early rheumatoid arthritis-results from study of new onset rheumatoid arthritis and Ontario best practices initiative	Not prediction of treatment response
Alemao (2016)[334]	Effects of achieving target measures in rheumatoid arthritis on functional status, quality of life, and resource utilization: analysis of clinical practice data	Not early RA
Alessandri (2004)[335]	Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement	Disease duration at baseline not reported
Aletaha (2007)[336]	Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients	No eligible factor/end point (DAS28 data not reported)
Aletaha (2009)[337]	Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment	No baseline predictors
Aletaha (2013)[338]	Rituximab dissociates the tight link between disease activity and joint damage in rheumatoid arthritis patients	Not prediction of treatment response
Aletaha (2013)[124]	Rheumatoid factor determines structural progression of rheumatoid arthritis dependent and independent of disease activity	Not prediction of treatment response
Alivernini (2014)[339]	Ultrasonography as useful tool to identify rheumatoid arthritis patients in clinical remission for tapering or withdrawal TNFa blockers without disease relapse	Disease duration at baseline not reported

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Alivernini (2016)[340]	Tapering and discontinuation of TNF-alpha blockers without disease relapse using ultrasonography as a tool to identify patients with rheumatoid arthritis in clinical and histological remission	Not early RA
Allaart (2006)[341]	Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study	No data on prediction of treatment response
Allaart (2010)[342]	When to start which DMARDs in rheumatoid arthritis?	Not possible to obtain paper
Allaart (2011)[126]	A multi-biomarker disease activity (Vectra DA) algorithm score for rheumatoid arthritis predicts radiographic progression in the BeSt study	Not prediction of treatment response
Ammitzbøll (2012)[343]	M-ficolin, an activator of the complement system, predicts DAS28 remission in early DMARD-naive rheumatoid arthritis	Not prediction of treatment response
Ammitzbøll (2012)[344]	M-ficolin, an activator of the complement system, is the strongest predictor of both DAS28 remission and low disease activity in a cohort of 180 early DMARD naive rheumatoid arthritis patients followed in the opera-study	Not prediction of treatment response
Ammitzbøll (2013)[345]	M-ficolin, an activator of the complement system, predicts DAS28 remission in early DMARD naive rheumatoid arthritis	Not prediction of treatment response
Ammitzbøll (2013)[346]	M-ficolin levels reflect disease activity and predict remission in early rheumatoid arthritis	Not prediction of treatment response
Ancuta (2014)[347]	Correlation between time to switch and clinical response amplitude to rituximab in second line treatment in rheumatoid arthritis patients with treatment failure to tumor necrosis factor inhibitors: 3-year data from repeat observational study	No relevant predictive factors
Anderson (2000)[128]	Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration	Not early RA
Angwin (2006)[348]	Radiographic progression in the Cobra study: computer measurements of joint space, a comparison with scoring	Not possible to obtain paper
Atzeni (2009)[349]	Predicting response to anti-TNF treatment in rheumatoid arthritis patients	Not early RA
Atzeni (2014)[350]	Predictors of response to anti-TNF therapy in RA patients with moderate or high DAS28 scores	Not early RA
Baddoura (2006)[351]	Severity of rheumatoid arthritis: the SEVERA study	Not prediction of treatment response and no eligible predictive factor
Baer (2014)[352]	Does low disease activity at six months predict remission at 12 months in rheumatoid arthritis patients treated with biologics in a real-world setting?	Not prediction of treatment response
Baillet (2014)[353]	Biomarker sets predict therapeutic response to TNF-inhibitors in rheumatoid arthritis and spondyloarthritis patients: a theragnostic approach in a multicenter cohort	Results not reported separately for RA patients on relevant predictors
Bakker (2010)[130]	Development of a multi-biomarker test for rheumatoid arthritis (RA) disease activity (Vectra DA)	Not prediction of treatment response
Balogh (2013)[354]	Comparison of DAS-28 and 2011-ACR/EULAR remission criteria in a biologic-treated rheumatoid arthritis patient cohort	Not early RA
Balogh (2013)[355]	Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder	Not early RA

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Balsa (2010)[129]	Prediction of functional impairment and remission in rheumatoid arthritis patients by biochemical variables and genetic polymorphisms	Not early RA
Barnabe (2011)[356]	Predictors for remission in rheumatoid arthritis are affected by remission definition	Not early RA
Barnabe (2012)[357]	Identified predictors for remission in rheumatoid arthritis depend on remission definition	Not early RA
Barnabe (2014)[358]	The effect of different remission definitions on identification of predictors of both point and sustained remission in rheumatoid arthritis treated with anti-TNF therapy	Not early RA
Baruth (2013)[359]	Factors associated with disability in a sample of adults with arthritis	Not early RA
Bathon (2005)[360]	Disease activity scores using CRP versus ESR and the relationship between EULAR and ACR responses in patients with early rheumatoid arthritis	Not prediction of treatment response
Baumgartner (2004)[361]	Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability	Not early RA
Bay-Jensen (2014)[362]	Serological biomarkers of joint tissue turnover predict tocilizumab response at baseline	Not early RA
Bejarano (2012)[363]	Relationship between early bone mineral density changes and long-term function and radiographic progression in rheumatoid arthritis	No relevant predictive factors
Bellis (2015)[364]	Ultrasound-detected synovitis and tenosynovitis independently associate with flare in patients with rheumatoid arthritis in clinical remission	Not early RA
Ben Slama (2014)[365]	Comparison of activity score DAS28-ESR and DAS28-CRP in patients with rheumatoid arthritis	Not early RA
Benedict (2010)[366]	Comparative effectiveness of biologic therapies for treating rheumatoid arthritis (RA) in patients who failed an anti tumor necrosis factor agent: a meta-regression analysis	Not early RA
Bentzon (1986)[367]	Influence of previous gold treatment and other patient variables on outcome of treatment with disease modifying anti-rheumatic drugs (DMARD) in patients with rheumatoid arthritis	Not early RA
Benucci (2010)[368]	Predictive factors of response to rituximab therapy in rheumatoid arthritis: what do we know today?	Review (not systematic)
Bijlsma (2007)[369]	Optimal use of methotrexate: the advantages of tight control	Editorial
Bingham (2012)[370]	Predictors of significant Disease Activity Score-28 (using CRP) remission achieved with intravenous golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results of the phase 3, multicenter, double-blind, placebo-controlled trial	Not early RA
Bingham (2013)[371]	Predictors of significant Disease Activity Score-28 (using C-reactive protein) remission achieved with intravenous golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results of the phase III, multicentre, double-blind, placebo-controlled trial	Not early RA
Bobbio-Pallavicini (2007)[372]	High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Boers (2001)[373]	Inflammation and damage in an individual joint predict further damage in that joint in patients with early rheumatoid arthritis	Not prediction of treatment response
Borangiu (2014)[374]	Ultrasound active synovitis can be predicted by using clinical measures	Disease duration at baseline not reported
Bouman (2015)[375]	Associations of a multi-biomarker disease activity score with clinical and radiographic parameters in rheumatoid arthritis	Not prediction of treatment effect
Braun (2008)[376]	Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomised, double-blind, controlled, phase IV trial	No relevant outcomes
Breedveld (2005)[377]	Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis	Not early RA
Brown (2002)[378]	Baseline clinical, functional and ultrasonographic assessment can be used to predict subsequent remission in rheumatoid arthritis	Disease duration at baseline not reported
Buch (2003)[379]	Does synovial cytokine expression predict response to tumour necrosis factor-alpha blockade in patients with rheumatoid arthritis?	Not prediction of treatment response
Buchanan (2013)[380]	Basal metabolic rate as an indicator of rheumatoid arthritis disease activity and predictor of remission: Australian results from period 1 of the preserve trial	Disease duration at baseline not reported
Burmester (2008)[381]	Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study	Not early RA
Burmester (2015)[382]	Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial	Not prediction of treatment effect
Bykerk (2015)[383]	On drug and drug-free remission by baseline disease duration in the avert trial: abatacept versus methotrexate comparison in patients with early rheumatoid arthritis	Insufficient detail of baseline characteristics
Callaghan (2014)[384]	Biological therapy for rheumatoid arthritis: is personalised medicine possible?	Not early RA
Cañete (2011)[385]	Clinical significance of high levels of soluble tumour necrosis factor-alpha receptor-2 produced by alternative splicing in rheumatoid arthritis: a longitudinal prospective cohort study	No relevant predictive factors
Canhão (2012)[386]	Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis	Not early RA
Cantini (2016)[387]	Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis	Not early RA
Capell (1993)[388]	Second line (disease modifying) treatment in rheumatoid arthritis: which drug for which patient?	Not prediction of treatment response
Castrejón (2016)[389]	Prediction of remission in a French early arthritis cohort by RAPID3 and other core data set measures, but not by the absence of rheumatoid factor, anticitrullinated protein antibodies, or radiographic erosions	Not prediction of treatment response
Casu (2013)[390]	Clinical and serological response to tocilizumab in patients with rheumatoid arthritis	Not early RA
Cavet (2009)[391]	Predicting radiographic progression in rheumatoid arthritis with ultrasound and biomarkers	Disease duration at baseline not reported
Cazzato (2014)[392]	Early response indicator early predicts clinical response to certolizumab in rheumatoid arthritis patients	Disease duration at baseline not reported

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Chandrashekara (2015)[393]	Neutrophil–lymphocyte ratio, pain perception, and disease activity score may serve as important predictive markers for sustained remission in rheumatoid arthritis	Not prediction of treatment response
Chatzidionysiou (2011)[394]	Seropositivity and in particular ACPA positivity is a strong predictor of response to treatment with rituximab: pooled data from 10 European registries	Not possible to obtain paper
Chatzidionysiou (2013)[395]	Seropositivity and response to RTX: data from the cererra collaboration	Disease duration at baseline not reported
Chatzidionysiou (2015)[396]	Smoking and response to rituximab in anti-CCP positive and negative rheumatoid arthritis-results from an international European collaboration	Not early RA
Chen (2013)[397]	Influence of adult height on rheumatoid arthritis: association with disease activity, impairment of joint function and overall disability	No relevant predictive factors
Chen (2014)[398]	Elevated serum IgG4 defines specific clinical phenotype of rheumatoid arthritis	Not early RA
Cheung (2014)[399]	Are tender joints better than synovitis to predict structural damage in rheumatoid arthritis?	Not early RA
Chitale (2012)[400]	Initial triple DMARD therapy predicts ACR EULAR remission in an early rheumatoid arthritis inception cohort	Not prediction of treatment response
Cho (2012)[401]	Do patients with elderly-onset rheumatoid arthritis have severe functional disability?	Not early RA
Choquette (2010)[402]	Impact of disease duration on the outcome of RA patients treated with infliximab in Canada	Not early RA
Choquette (2011)[403]	Comparison of disease characteristics of rheumatoid arthritis patients in remission according to the DAS criteria versus the new ACR/EULAR criteria in a real-world patient population	Not possible to obtain paper
Choquette (2013)[404]	Comparison of disease characteristics of RA patients in remission according to the DAS criteria versus the new ACR/EULAR criteria in a real-world patient population	Not early RA
Choquette (2013)[405]	What is the impact of rheumatoid factor positivity on the real-world effectiveness of infliximab treatment in rheumatoid arthritis?	Disease duration at baseline not reported
Choquette (2015)[406]	Use of rituximab compared to anti-TNF agents as second and third line therapy in patients with rheumatoid arthritis: 6-year follow-up report from the rhumadata clinical database and registry	No relevant predictive factors or outcomes
Choquette (2015)[407]	Predictors of clinical response to biologics in rheumatoid arthritis: experience from a Canadian clinic	Not early RA
Chow (2015)[408]	What is the effect of TNF inhibitors on employment status in rheumatoid arthritis patients and what are the predictors of progression to unemployment?	Disease duration at baseline not reported
Choy (2007)[409]	Does the Health Assessment Questionnaire predict 5-year quality of life in early RA?	Commentary
Choy (2013)[410]	Physician global assessment at three months is strongly predictive of disease activity at 12 months in early rheumatoid arthritis. Results from the catch cohort	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Christensen (2014)[411]	Temporal summation of pain and ultrasound Doppler activity as predictors of treatment response in patients with rheumatoid arthritis: protocol for the Frederiksberg hospitals Rheumatoid Arthritis, pain assessment and Medical Evaluation (FRAME-cohort) study	Protocol
Christensen (2016)[412]	Ultrasound Doppler but not temporal summation of pain predicts DAS28 response in rheumatoid arthritis: a prospective cohort study	Not early RA
Ciurtin (2015)[413]	Evaluating impact of risk associated outcomes on ultrasound Doppler score of patients with inflammatory hand joint pain using a beta-binomial model	Insufficient detail reported
Ciurtin (2016)[149]	Ultrasound-detected subclinical inflammation was better reflected by the disease activity score (DAS-28) in patients with suspicion of inflammatory arthritis compared to established rheumatoid arthritis	Not prediction of treatment response
Coburn (2015)[414]	Anti-citrullinated protein antibody and radiographic disease progression in rheumatoid arthritis	Disease duration at baseline not reported
Cohen (2005)[415]	C-reactive protein predicts treatment response to adalimumab (HUMIRA (R)) in patients with rheumatoid arthritis	Not possible to obtain paper
Colmegna (2016)[416]	High rates of obesity and greater associated disability among people with rheumatoid arthritis in Canada	Not early RA
Combe (2001)[62]	Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study	Not prediction of treatment response
Couderc (2013)[417]	Predictive factors of rituximab response in rheumatoid arthritis: results from a French university hospital	Not early RA
Couderc (2013)[417]	Predictive factors for the response to rituximab in rheumatoid arthritis: results from a French university hospital	Not early RA
Courvoisier (2016)[418]	Rheumatoid arthritis patients after initiation of a new biologic agent: trajectories of disease activity in a large multinational cohort study	Not early RA
Cuchacovich (2008)[419]	Basal anti-cyclic citrullinated peptide (anti-CCP) antibody levels and a decrease in anti-CCP titres are associated with clinical response to adalimumab in rheumatoid arthritis	Not early RA
Cuppen (2015)[420]	Personalized biological treatment for rheumatoid arthritis: a systematic review with a focus on clinical applicability	Not early RA
Cuppen (2015)[421]	Towards individualized risk determination in RA: a prediction model for TNFi discontinuation within the first year after start	Insufficient detail reported
Cuppen (2016)[422]	Exploring the inflammatory metabolomic profile to predict response to TNF-alpha inhibitors in rheumatoid arthritis	Not early RA
Curtis (2010)[155]	Validation of a multi-biomarker test for rheumatoid arthritis (RA) disease activity (Vectra DA) in a multi-cohort study	Insufficient information to determine treatment response
Curtis (2010)[423]	Prediction of one-year response to etanercept and methotrexate in rheumatoid arthritis patients in TEMPO	Not early RA
Curtis (2011)[424]	Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis	No relevant predictors
Curtis (2011)[425]	Validation of a preliminary administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis	No relevant predictors
Curtis (2012)[426]	Predicting future response to certolizumab pegol in rheumatoid arthritis patients: features at 12 weeks associated with low disease activity at 1 year	Not early RA

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Curtis (2012)[156]	Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity	Treatment duration of < 6 months
Curtis (2013)[427]	Clinical response within 12 weeks as a predictor of future low disease activity in patients with early RA: results from the TEAR Trial	No relevant predictors
Curtis (2015)[157]	A randomized trial comparing disease activity measures for the assessment and prediction of response in rheumatoid arthritis patients initiating certolizumab pegol	Not early RA
D'Agostino (2015)[428]	Do ultrasound (power Doppler ultrasonography) and Disease Activity Score-28 measure different aspects of disease activity? Analyses from an open-label study of power Doppler ultrasonography response patients with rheumatoid arthritis patients starting abatacept	Nothing on prediction of treatment effect
D'Agostino (2015)[429]	In patients with rheumatoid arthritis and an inadequate response to methotrexate, does body mass index influence the efficacy of abatacept on inflammation when measured by power Doppler ultrasonography? Results from the appraise study	Not early RA
Dahl (2009)[430]	TNF-inhibitors in established rheumatoid arthritis: the effect of age on treatment response and predictors of remission	No baseline disease duration reported
Dai (2010)[431]	The clinical response to etanercept in rheumatoid arthritis is in part dependent on pretreatment tumour necrosis factor-alpha expression in the synovium	Not possible to obtain paper
Daïen (2014)[432]	Predictive factors of response to biological disease modifying antirheumatic drugs: towards personalized medicine	Review (not systematic)
Dames (2006)[433]	Utility of Disease Activity Score-28 (DAS-28) for determining need for DMARD change in veterans affairs rheumatoid arthritis (VARA) patients: an analysis of discrepancies between DAS-28 scores and clinical stability status	Not prediction of treatment response
da Mota (2012)[434]	Baseline HAQ and SF-36 questionnaire scores cannot predict clinical remission, radiographic progression or the need for biological therapy in a three-year prospective study of a Brazilian early rheumatoid arthritis cohort	Not prediction of treatment response
Danve (2015)[435]	Male gender and higher hemoglobin predict response to methotrexate in rheumatoid arthritis	No relevant predictive factors or outcomes
Darawankul (2015)[436]	The good EULAR response at the first year is strongly predictive of clinical remission in rheumatoid arthritis: results from the TARAC cohort	Not early RA
Dasgupta (2014)[437]	Predictors of low disease activity and remission after one dose of golimumab in patients with rheumatoid arthritis	Not early RA
Dejaco (2010)[438]	Third generation anti-cyclic citrullinated peptide antibodies do not predict anti-TNF-alpha treatment response in rheumatoid arthritis	Disease duration unclear
de Jong (2013)[439]	Response to glucocorticoids at 2 weeks predicts the effectiveness of DMARD induction therapy at 3 months: post hoc analyses from the tREACH study	Treatment duration of < 6 months at time of analysis
de Jong (2015)[440]	Effect of prednisone on type I interferon signature in rheumatoid arthritis: consequences for response prediction to rituximab	Not early RA
de Miguel (2015)[441]	Doppler ultrasound better predicts X-Ray progression in rheumatoid arthritis than any definition of clinical remission	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
de Rooy (2011)[442]	Predicting arthritis outcomes-what can be learned from the Leiden Early Arthritis Clinic?	Not prediction of treatment response
de Vries-Bouwstra (2006)[65]	Using predicted disease outcome to provide differentiated treatment of early rheumatoid arthritis	Not prediction of treatment response
de Vries-Bouwstra (2008)[161]	Progression of joint damage in early rheumatoid arthritis: association with HLA–DRB1, rheumatoid factor, and anti–citrullinated protein antibodies in relation to different treatment strategies	Time of predictor measurement not stated and unclear whether or not it was within the 2-year early RA window
Demir (2003)[443]	Value of wrist ultrasound in prediction of disease activity in patients with rheumatoid arthritis	Not possible to obtain paper
Di Cicco (2014)[444]	Synovial ectopic lymphoneogenesis predicts primary clinical response to certolizumab pegol in patients with rheumatoid arthritis	Not early RA
Di Cicco (2014)[445]	Presence of synovial lymphocyte aggregates predicts clinical response to DMARD therapy in patients with early rheumatoid arthritis	Not prediction of treatment response
Ding (2015)[446]	Predictors of response to TNF-α antagonist therapy in Chinese rheumatoid arthritis	No relevant outcomes
Dirven (2009)[447]	Predictors of HAQ response after 3 months of treatment with different strategies in recent onset active RA	Not prediction of treatment response
Dougados (2007)[448]	Sustained efficacy along with improvements in disease activity score 28 (DAS 28) and patient (Pt)-reported outcomes (PROs) with abatacept (Aba) in rheumatoid arthritis (RA) pts with an inadequate response to anti-tumor necrosis factor (TNF) therapy: the long-term extension (LTE) of the attain trial	Not prediction of treatment response
Drouin (2010)[449]	Predictors of clinical response and radiographic progression in patients with rheumatoid arthritis treated with methotrexate monotherapy	Not early RA
Durez (2014)[450]	Baseline predictors of remission rates during golimumab treatment for rheumatoid arthritis in the go-more study	Not early RA
Ellingsen (2009)[451]	The increased cc chemokine ligand 19 (CCL19) at baseline is an independent predictor of the 5-year radiographic progression in early steroid and DMARD-naive rheumatoid arthritis (RA) patients	Insufficient information to determine treatment response
Emery (2006)[452]	Abatacept inhibits structural damage progression, as assessed by the Genant-modified Sharp scoring system, in Rheumatoid Arthritis (RA) patients with an inadequate response to Methotrexate (MTX): the aim (abatacept in inadequate responders to MTX) trial – a sub-analysis by disease duration	Not possible to obtain paper
Emery (2011)[453]	Exploratory analyses of the association of MRI with clinical, laboratory and radiographic findings in patients with rheumatoid arthritis	Not prediction of treatment effect
Emery (2011)[454]	Optimising treatment in rheumatoid arthritis: a review of potential biological markers of response	Review (not systematic)
Emery (2011)[455]	Post-treatment changes in serum C-reactive protein levels and clinical response in rheumatoid arthritis	Not early RA
Emery (2012)[456]	Combination etanercept and methotrexate provides better disease control in very early (≤ 4 months) versus early rheumatoid arthritis (> 4 months and < 2 years): post hoc analyses from the COMET study	Does not meet criteria for the window of opportunity covariate (not all patients DMARD naive)

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Emery (2012)[457]	Golimumab's efficacy in patients with very active disease in methotrexate-naive rheumatoid arthritis	Not early RA
Emery (2012)[458]	Predictors of radiographic progression in methotrexate-naive patients with rheumatoid arthritis based on one-year radiographic data from the go-before golimumab clinical trial	Not early RA
Emery (2013)[459]	Radiographic progression in patients with early rheumatoid arthritis treated with etanercept: results from the prize study	Not prediction of treatment response
Emery (2014)[460]	Early response to etanercept-methotrexate induction therapy predicts sustained remission with reduced–dose combination regimen in the prize study	Insufficient methodological details reported
Emery (2014)[461]	Early response to full-dose etanercept-plus-methotrexate induction therapy predicts sustained remission with reduced-dose combination therapy in early rheumatoid arthritis patients	Insufficient methodological details reported
Emery (2014)[462]	Efficacy of golimumab plus methotrexate in methotrexate-naive patients with severe active rheumatoid arthritis	Not early RA
Emery (2014)[463]	Predictors of drug-free remission following treatment with abatacept (in combination with methotrexate or as monotherapy) in early rheumatoid arthritis	No relevant outcomes
Emery (2015)[464]	Abatacept plus methotrexate can effectively and safely regain the target of remission following re-treatment for flares after drug-free withdrawal in patients with early rheumatoid arthritis	Not prediction of treatment effect
Emery (2015)[465]	A European chart review study on early rheumatoid arthritis treatment patterns, clinical outcomes, and healthcare utilization	Not early RA
Emery (2015)[116]	Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period	No relevant outcome
Erickson (2014)[466]	Predictors of radiologic disease progression during the rheumatoid arthritis comparison of active therapies trial	Not early RA
Eser (2012)[467]	Extraarticular manifestations in Turkish patients with rheumatoid arthritis: impact of EAMs on the health-related quality of life in terms of disease activity, functional status, severity of pain, and social and emotional functioning	Not early RA Not prediction of treatment effect
Estrach (2003)[468]	Swollen joint count as a predictor of response to anti-tumor necrosis factor alpha therapy in rheumatoid arthritis: comment on the article by Sokka and Pincus (multiple letters) [3]	Not early RA
Fabricio (2015)[469]	Predictability to achieve low activity and/or remission with leflunomide use in patients with rheumatoid arthritis	Insufficient methodological details reported
Fabris (2010)[470]	Study on the possible role of the –174G>C IL-6 promoter polymorphism in predicting response to rituximab in rheumatoid arthritis	Not early RA
Fautrel (2012)[471]	Moderate rheumatoid arthritis despite methotrexate treatment: risk of radiographic progression	Not early RA
Fautrel (2016)[472]	Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study)	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Favalli (2013)[473]	Disease duration and year of publication affect the results of studies on rheumatoid arthritis damage progression by biologic agents: a systematic review and meta-analysis	Not prediction of treatment response
Favalli (2014)[474]	The comparison of effects of biologic agents on rheumatoid arthritis damage progression is biased by period of enrolment: data from a systematic review and meta-analysis	Not prediction of treatment response
Fedele (2015)[475]	Clinical parameters and B cell subsets as biomarkers of response to tocilizumab in rheumatoid arthritis	Insufficient detail reported
Fedorenko (2014)[476]	Effects of four different treatment regimens on radiologic progression in early rheumatoid arthritis (RA)	Insufficient detail reported on methods and results relating to prediction of treatment response
Feist (2010)[477]	A study to evaluate the effectiveness and safety of the interleukin-6 (IL-6) receptor antagonist tocilizumab (TCZ) after 4 and 24 weeks in patients with active rheumatoid arthritis (RA) final effectiveness results of the TAMARA study	Not prediction of treatment response
Ferdousi (2011)[478]	Disease duration as a determinate factor of disease activity and radiographic progression in rheumatoid arthritis	Pooled data from 2 trials (not risk model)
Fernández-Nebro (2007)[479]	Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis	Not early RA
Filer (2010)[480]	Utility of ultrasound joint counts as predictors of outcome in patients with very early arthritis	Not prediction of treatment response
Filippi (2015)[481]	Predictors of persistence of power Doppler ultrasound synovitis in rheumatoid arthritis patients in clinical remission	Not early RA
Finckh (2007)[482]	Cigarette smoking and radiographic progression in rheumatoid arthritis	Not early RA
Finckh (2010)[483]	Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumor necrosis factor (TNF) agents after previous failure of an anti-TNF agent?	Not early RA
Finckh (2015)[484]	The impact of tobacco smoking on the effectiveness of abatacept in rheumatoid arthritis: data from a pan European analysis of RA registries	Not early RA
Fisher (2011)[485]	Fine specificity of anti-citrullinated peptide antibodies is associated with response to anti-TNF agents in rheumatoid arthritis: results from the British Society of Rheumatology biologics register	Disease duration at baseline not reported
Fisher (2012)[486]	Heterogeneity of anticitrullinated peptide antibodies and response to anti-tumour necrosis factor agents in rheumatoid arthritis	Not early RA
Fleischmann (2014)[487]	Short-term efficacy of etanercept plus methotrexate vs. combinations of disease-modifying anti-rheumatic drugs with methotrexate in established rheumatoid arthritis	Not early RA
Folkersen (2016)[488]	Integration of known DNA, RNA and protein biomarkers provides prediction of anti-TNF response in rheumatoid arthritis: results from the COMBINE study	No relevant predictors
Foltz (2009)[489]	Ultrasound and magnetic resonance imaging did not provide early assessment of biotherapy response in patients with rheumatoid arthritis	Not prediction of treatment response

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Forsblad-d'Elia (2015)[490]	Drug adherence, response and predictors thereof for tocilizumab in patients with rheumatoid arthritis: results from the Swedish biologics register	Not early RA
Forslind (2007)[169]	Sex: a major predictor of remission in early rheumatoid arthritis?	Not prediction of treatment response
Fransen (2012)[491]	Clinical pharmacogenetic model to predict response of MTX monotherapy in patients with established rheumatoid arthritis after DMARD failure	Not early RA
Fujimura (2014)[492]	Predicting future response to tumor necrosis factor inhibitors by the distribution of affected joints in rheumatoid arthritis patients	Not early RA
Furst (2015)[493]	Evaluation of patient-reported outcomes by baseline disease duration: 6-month data from two clinical trials of patients with early rheumatoid arthritis treated with abatacept	No relevant predictive factors
Furst (2015)[494]	Final 10-year effectiveness and safety results from study DE020: adalimumab treatment in patients with rheumatoid arthritis and an inadequate response to standard therapy	Not early RA
Furuya (2013)[495]	Effect of TNF antagonists on the productivity of daily work of patients with rheumatoid arthritis	Not early RA
Gardette (2013)[496]	High level of anti-CCP antibodies is predictive of good response to rituximab in patients with active rheumatoid arthritis	Not early RA
Gherghe (2016)[497]	Association of the different types of radiographic damage with physical function in patients with rheumatoid arthritis: analysis of the RAPID trials	Not early RA
Giacomelli (2013)[498]	Mathematical model to predict the early responders in a monocentric cohort of patients with rheumatoid arthritis treated by anti TNFalpha	Insufficient detail reported
Glave-Testino (1994)[499]	Factors associated with disease severity in Mexican patients with rheumatoid arthritis	Not early RA
Goetz (2011)[500]	Review of treatment response in rheumatoid arthritis: assessment of heterogeneity	Not early RA
Gomez (2004)[501]	High titres of anti-CCP antibodies at baseline and after one year of DMARDs may predict a poor clinical response in patients with early rheumatoid arthritis	Not possible to obtain paper
González-Alvaro (2007)[502]	Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists	Not early RA
Gonzalez-Lopez (2014)[503]	Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) relation with extra-articular manifestations in rheumatoid arthritis	Not early RA No relevant outcomes
Goodman (2015)[504]	Body mass index is an independent risk factor for not achieving sustained remission in early rheumatoid arthritis: results from the catch observational study	Insufficient methods detail on assessment of prediction of treatment response
Goronzy (2004)[176]	Prognostic markers of radiographic progression in early rheumatoid arthritis	Not prediction of treatment response
Gottenberg (2012)[505]	Serum IL-6 and IL-21 are associated with markers of B cell activation and structural progression in early rheumatoid arthritis: results from the ESPOIR cohort	No relevant predictive factors
Graudal (2000)[506]	Inflammatory patterns in rheumatoid arthritis estimated by the number of swollen and tender joints, the erythrocyte sedimentation rate, and hemoglobin: long term course and association to radiographic progression	Not prediction of treatment response

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Gremese (2013)[507]	Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study	Not prediction of treatment response
Gremese (2015)[508]	Clinical and B cell subsets biomarkers of response to tocilizumab in rheumatoid arthritis	Not early RA
Gullick (2012)[509]	Predicting ongoing active disease in early rheumatoid arthritis using clinical measures	Pooled data from two trials (not risk model)
Hall (1991)[510]	Rheumatoid nodules do not predict response to treatment with slow-acting anti-rheumatic drugs	Not early RA
Hama (2012)[511]	Power Doppler ultrasonography is useful for assessing disease activity and predicting joint destruction in rheumatoid arthritis patients receiving tocilizumab-preliminary data	Not early RA
Hama (2014)[512]	PD signal detected by ultrasonography relates to joint destruction in rheumatoid arthritis under biologics therapy in real world	Not early RA
Hama (2015)[513]	Wrist PD signal detected by ultrasonography relates to joint destruction in rheumatoid arthritis under biologics therapy in real world	Not early RA
Hamann (2016)[514]	Factors associated with sustained remission in rheumatoid arthritis in patients treated with anti-tumor necrosis factor (anti-TNF)	Not early RA
Hambardzumyan (2013)[183]	A multi-biomarker disease activity score correlates with radiographic progression in early rheumatoid arthritis: results from a randomized trial	Not prediction of treatment response
Hambardzumyan (2013)[182]	A multi-biomarker disease activity blood test (Vectra DA) correlates with radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial	Not prediction of treatment response
Hambardzumyan (2013)[185]	In early rheumatoid arthritis, the 12 individual biomarkers that comprise the multiple biomarker disease activity score relate differentially to clinical response and radiographic progression: results from a randomized trial	Not prediction of treatment response
Hambardzumyan (2013)[184]	Multi-biomarker disease activity (MBDA) score and the 12 individual biomarkers in early rheumatoid arthritis patients relate differentially to clinical response and radiographic progression: results from the SWEFOT trial	Not prediction of treatment response
Hambardzumyan (2015)[515]	Predictive biomarkers for response or non-response to MTX monotherapy in early RA	No relevant predictive factors
Hammer (2010)[516]	A 78-joints ultrasonographic assessment is associated with clinical assessments and is highly responsive to improvement in a longitudinal study of patients with rheumatoid arthritis starting adalimumab treatment	Not early RA
Hammer (2011)[517]	Patients with rheumatoid arthritis on anti-TNF therapy; responders with major reduction in power Doppler activity can be identified after one month	Not early RA
Haney (2012)[518]	Correlation of a multi-biomarker disease activity response assessment to disease activity score 28 (C-reactive protein) response assessment and OMERACT RAMRIS scores in a placebo-controlled rheumatoid arthritis clinical trial with abatacept (ASSET)	Treatment duration of < 6 months
Haroon (2008)[519]	Tailor-made therapy in rheumatoid arthritis: fact or fiction?	Review (not systematic)
Harris (2012)[520]	Can we improve outcomes in early rheumatoid arthritis by determining best practices? An analysis of the Canadian early rheumatoid arthritis cohort (CATCH)	Not prediction of treatment response

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Harris (2013)[521]	Can we improve outcomes in early rheumatoid arthritis (ERA) by determining best practices? An analysis of the Canadian era cohort (CATCH)	Not prediction of treatment response
Hazlewood (2015)[522]	Enhancing comparative effectiveness research by combining observational and randomized trial data to personalize the choice between methotrexate and triple therapy for methotrexate-naive patients with early rheumatoid arthritis	No relevant outcome
Heidari (2007)[523]	The value of changes in CRP and ESR for predicting treatment response in rheumatoid arthritis	Not early RA
Heimans (2011)[524]	Body mass index is associated with decreased response to initial and delayed treatment with dose escalated infliximab in patients with recent onset rheumatoid arthritis	Insufficient detail reported on methods and results relating to prediction of treatment response
Heimans (2014)[91]	A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study	Not prediction of treatment response
Hernandez (2013)[525]	Predictive factors of response to tocilizumab in patients with active rheumatoid arthritis	Not early RA
Herold (2015)[526]	Efficacy of tocilizumab monotherapy in patients with RA is not influenced by ACPA positivity	Insufficient reporting of results
Hetland (2010)[527]	Radiographic progression and remission rates in early rheumatoid arthritis – MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial	Not prediction of treatment response
Hirano (2015)[528]	Predictors of effectiveness in golimumab treatment and efficacy of dose-escalation of golimumab in patients with rheumatoid arthritis-a multicenter registry study TBCR	Not early RA
Hirata (2013)[529]	Repeated high or low multi-biomarker disease activity (Vectra® DA algorithm) scores associated with radiographic outcomes in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors	Not early RA
Hirata (2015)[530]	Serum 14–3–η level is associated with severity and clinical outcomes of rheumatoid arthritis, and its pretreatment level is predictive of DAS28 remission with tocilizumab	Not early RA
Hoekstra (2003)[531]	Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis	Not early RA
Horton (2016)[532]	Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment-to-target strategy	Not prediction of treatment response
Hoshi (2011)[533]	Greater physical dysfunction is a negative predictor for achieving Boolean-based remission in patients with rheumatoid arthritis treated with tocilizumab	Not early RA
Hu (2011)[534]	Population approach for exposure–response modelling of golimumab in patients with rheumatoid arthritis	Not early RA
Huizinga (2011)[535]	Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression – commentary	Not possible to obtain paper
Iagnocco (2015)[536]	Power Doppler ultrasound monitoring of response to anti-tumor necrosis factor alpha treatment in patients with rheumatoid arthritis	Not early RA

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TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Iannaccone (2011)[537]	Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study	Not early RA
Iannone (2013)[538]	Etanercept therapy in rheumatoid arthritis patients with moderate or severe disease activity	Not early RA
Iannone (2015)[539]	Early good EULAR response predicts low/remission disease state in rheumatoid arthritis patients on treatment with certolizumab in real life settings. Data from Italian registry GISEA	Not early RA
Ickinger (2011)[540]	Predictors of joint damage in South Africans with rheumatoid arthritis	Not early RA
Ideguchi (2006)[541]	Bone erosions in rheumatoid arthritis can be repaired through reduction in disease activity with conventional disease-modifying antirheumatic drugs	Not early RA
Inanc (2013)[542]	Can ultrasonographic findings predict response to tumor necrosis factor-alpha inhibitor treatment in rheumatoid arthritis?	Not early RA
Inanc (2014)[543]	Ultrasonographic assessment of joint inflammation in rheumatoid arthritis: predictive value in response to tumor necrosis factor-a inhibitor treatment	Not early RA
Inanc (2014)[544]	Ultrasonographic assessment of joint inflammation in rheumatoid arthritis: predictive value in response to tumor necrosis factor-alpha inhibitor treatment	Not early RA
Inanc (2016)[545]	Predictive value of ultrasonographic assessment of disease activity in response to tumor necrosis factor-alpha inhibitor treatment in rheumatoid arthritis: a prospective cohort study	Not early RA
Inoue (2009)[546]	Preliminary study to identify the predictive factors for the response to methotrexate therapy in patients with rheumatoid arthritis	Not early RA
Inoue (2015)[547]	Effect of smoking on remission proportions differs between male and female patients with rheumatoid arthritis: a study based on the IORRA survey	Not early RA
Isaacs (2009)[548]	Autoantibody-positive rheumatoid arthritis (RA) patients (PTS) have enhanced clinical response to rituximab (RTX) when compared with seronegative patients	Not possible to obtain paper
Isaacs (2013)[549]	Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis	Not early RA
Ishiguro (2016)[550]	Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naive patients with rheumatoid arthritis: the FIRST Bio study	Not early RA
Iwamoto (2009)[551]	Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population	Not early RA
Iwamoto (2016)[552]	Evaluation of switching from intravenous to subcutaneous formulation of tocilizumab in patients with rheumatoid arthritis	Not possible to obtain paper
Izumi (2015)[553]	Baseline serum osteopontin levels predict the clinical effectiveness of tocilizumab but not infliximab in biologic-naive patients with rheumatoid arthritis: a single-centre prospective study at 1 year (the Keio First-Bio Cohort Study)	Not early RA
Jansen (2001)[554]	Predictors of radiographic joint damage in patients with early rheumatoid arthritis	Not prediction of treatment response

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Jawaheer (2012)[555]	Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis – results from the DANBIO Registry	Not prediction of treatment response
Jayakumar (2012)[556]	Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS	Not prediction of treatment response
Jessome (2015)[557]	Does computerized segmentation of early erosions on magnetic resonance imaging predict functional ability in rheumatoid arthritis?	Not early RA
Jilani (2015)[558]	The role of citrullinated protein antibodies in predicting erosive disease in rheumatoid arthritis: a systematic literature review and meta-analysis	Not prediction of treatment response
Jones (1994)[559]	Factors predicting outcome in rheumatoid arthritis	Insufficient detail reported
Joo (2015)[560]	Clinical predictors of severe radiographic damage in Korean patients with rheumatoid arthritis	Insufficient details reported on methods and results for prediction of treatment response and model construction
Jurgens (2014)[561]	Contribution of the individual components of the disease activity score (DAS28) to the total DAS28 score among responders and non-responders to biological therapy for rheumatoid arthritis	No eligible predictive factors
Jurgens (2015)[562]	Contribution of the subjective components of the disease activity score to the response to biologic treatment in rheumatoid arthritis	No eligible predictive factors
Kameda (2013)[563]	Continuation/discontinuation of methotrexate and clinical response to etanercept determine the radiographic progression/repair in patients with rheumatoid arthritis: a subanalysis of 52-week results from the JESMR study	No relevant outcomes
Kameda (2013)[564]	A merged presentation of clinical and radiographic data using probability plots in a clinical trial, the JESMR study	Not early RA
Kaneko (2013)[565]	Predictors of clinical remission (DAS28CRP < 2.6) in patients with RA who were treated with abatacept	Disease duration at baseline not reported
Kaneshita (2015)[566]	Highly elevated rheumatoid factor is a risk factor for abatacept treatment failure in Japanese patients with rheumatoid arthritis	Not early RA
Kanters (2014)[567]	What drives the comparative effectiveness of biologics vs. methotrexate in rheumatoid arthritis? Meta-regression and graphical inspection of suspected clinical factors	No relevant outcome
Karateev (2015)[568]	Dynamics of disease activity scores during the first 12 weeks allow to predict the necessity in combination therapy with methotrexate and biologics within T2T strategy in patients with early and established rheumatoid arthritis (REMARCA study)	Not prediction of treatment effect
Kastbom (2016)[199]	Changes in the anticitrullinated peptide antibody response in relation to therapeutic outcome in early rheumatoid arthritis: results from the SWEFOT trial	Not prediction of treatment response
Katchamart (2010)[569]	Predictors for remission in rheumatoid arthritis patients: a systematic review	Not prediction of treatment response
Kawada (2016)[570]	Predictors of biological antirheumatic drug discontinuation in patients with rheumatoid arthritis while in remission	Comment (not study findings)
Kawasaki (2013)[571]	Shorter disease duration is important for tocilizumab to achieve Boolean remission	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Kawashiri (2013)[572]	Evaluation of the efficacy of tocilizumab toward the patients with active rheumatoid arthritis of Nagasaki Prefecture, Japan	Not early RA
Kawashiri (2014)[573]	Baseline low modified health assessment questionnaire (MHAQ) predicts the state of remission estimated by clinical disease activity index and MHAQ at 1 year in tocilizumab-treated rheumatoid arthritis patients	Not early RA
Kay (2014)[574]	Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year	Not early RA
Kekow (2010)[575]	Real life treatment with rituximab in TNF blocker non-responders is superior to treatment with a second TNF blocker	Not early RA
Khan (2012)[576]	Smoking and rheumatoid factor status in predicting responses to biologics	Not early RA
Kim (2016)[577]	No predictive effect of body mass index on clinical response in patients with rheumatoid arthritis after 24 weeks of biological disease-modifying antirheumatic drugs: a single-centre study	Not early RA
Kimura (2016)[578]	Time lag between the initiation of adalimumab after methotrexate correlates with the efficacy of adalimumab in rheumatoid arthritis patients	Not early RA
Klaasen (2009)[579]	Is the response to infliximab influenced by body mass index in rheumatoid arthritis patients?	Not early RA
Klaasen (2009)[580]	The relationship between synovial lymphocyte aggregates and the clinical response to infliximab in rheumatoid arthritis: a prospective study	Not early RA
Klaasen (2011)[581]	Body mass index and clinical response to infliximab in rheumatoid arthritis	Not early RA
Knudsen (2008)[205]	Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome	Not prediction of treatment response
Koike (2012)[582]	Safety and effectiveness responses to etanercept for rheumatoid arthritis in Japan: a sub-analysis of a post-marketing surveillance study focusing on the duration of rheumatoid arthritis	Not early RA
Koike (2014)[583]	Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan	Not early RA
Kojima (2011)[584]	Early aggressive intervention for rheumatoid arthritis increases rate of remission defined using a Boolean approach in clinical practice with tocilizumab	Not early RA
Kojima (2013)[585]	Importance of concomitant MTX use during treatment with tocilizumab in patients with rheumatoid arthritis	Not early RA
Kojima (2013)[586]	Relationship between physicians' decision to use concomitant glucocorticoid and remission during treatment with tocilizumab in patients with background of limited dose of MTX	Not early RA
Kojima (2014)[587]	Importance of methotrexate therapy concomitant with tocilizumab treatment in achieving better clinical outcomes for rheumatoid arthritis patients with high disease activity: an observational cohort study	Not early RA
Kojima (2015)[588]	Importance of both disease activity at 12 weeks and clinical response up to 12 weeks to predict achievement of low disease activity at 52 weeks during abatacept treatment in biologics-switching patients with rheumatoid arthritis: a multicenter observational cohort study in Japan	Not early RA

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Kojima (2015)[589]	Predictive factors for achieving low disease activity at 52 weeks after switching from tumor necrosis factor inhibitors to abatacept: results from a multicenter observational cohort study of Japanese patients	Not early RA
Kotak (2013)[590]	Characteristics of a moderate rheumatoid arthritis patient population who lost remission or low disease activity: data from the Consortium of Rheumatology Researchers of North America, Inc. (CORRONA)	Not early RA
Kovalchik (2012)[591]	An association study of disease activity score components and patient satisfaction with overall health for early RA patients on non-biologic DMARD therapy	No relevant outcome measure
Kristensen (2008)[592]	Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register	Not early RA
Kronisch (2016)[593]	Brief report: predicting functional disability: one-year results from the Scottish early rheumatoid arthritis inception cohort	Mixed RA and UA population with no separate analyses
Kruger (2012)[594]	Reduction in sickness absence in patients with rheumatoid arthritis receiving adalimumab: data from a German noninterventional study	Not early RA
Kumar (2002)[595]	Validation of an Indian version of the Health Assessment Questionnaire in patients with rheumatoid arthritis	Not prediction of treatment effect
Kume (2012)[596]	Anti-cyclic citrullinated protein antibodies as a predictor of response to tocilizumab in patients with rheumatoid arthritis a prospective study	No definition of duration of RA and no full text identified
Kuriya (2014)[597]	Earlier time to remission predicts sustained clinical remission in early rheumatoid arthritis – results from the Canadian Early Arthritis Cohort (CATCH). Predictors of sustained clinical remission in early rheumatoid arthritis-results from the Canadian early arthritis cohort	Not prediction of treatment response
Kuriya (2015)[598]	Working status and improvements in work productivity over time in an early rheumatoid arthritis (ERA) cohort	No baseline predictors (6 months)
Kynde (2014)[599]	Delay in RA diagnosis of more than 12 months is associated with deteriorated functional status in patients in bDMARD treatment-results from a prospective study	No definition of duration of RA
Lard (200)[600]	Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies	Not prediction of treatment response
Le Blay (2014)[601]	Progressive spacing tocilizumab infusions after remission in rheumatoid arthritis: the absence of erosion would be determinant in choosing this strategy	Not early RA
Lee (2008)[602]	Disease Activity Score (DAS) and Health Assessment Questionnaire (HAQ) values show similar changes from baseline to endpoint in clinical trials of biological agents in patients with rheumatoid arthritis (RA)	Not prediction of treatment response
Lee (2013)[603]	Application of a multi-biomarker disease activity (Vectra® DA) score for assessing rheumatoid arthritis patients with fibromyalgia or low C-reactive protein	Not prediction of treatment effect
Li (2015)[604]	Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Li (2015)[218]	Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis	Not prediction of treatment response [and median disease duration suggests not early RA – although it was an early RA (< 2 years) cohort]
Lie (2006)[605]	Predictors of response to methotrexate treatment: Results from a longitudinal observational study of 876 patients with RA [abstract]	Not prediction of treatment response
Lie (2011)[606]	Characterization of long-term responders to first treatment course of rituximab (RTX) results from the CERERRA collaboration	Not early RA
Lie (2011)[607]	Early versus delayed retreatment with rituximab (RTX) in relation to long term clinical response data from the CERERRA collaboration	No definition of duration of RA
Lie (2012)[608]	Effectiveness of sulfasalazine and methotrexate in 1102 DMARD-naive patients with early RA	Not prediction of treatment effect
Lima (2013)[609]	The influence of clinical and genetic variables on methotrexate effectiveness in Portuguese rheumatoid arthritis patients	Not early RA
Liu (2015)[610]	Impact of obesity on the disease course of rheumatoid arthritis	Insufficient detail reported
Ljung (2011)[611]	New assay generation for antibodies against modified and citrullinated peptides predicts poor response to TNF inhibitor therapy	Not early RA
Loppin (2010)[612]	Low rate of rheumatoid arthritis remission in real life: might predictive factors explain?	Incomplete definition of duration of disease and no full text identified
Lukas (2010)[613]	Repair of erosions occurs almost exclusively in damaged joints without swelling	Not early RA
Lv (2014)[614]	The status of rheumatoid factor and anti-cyclic citrullinated peptide antibody are not associated with the effect of anti-TNFA agent treatment in patients with rheumatoid arthritis: a meta-analysis	Not early RA
Ma (2009)[615]	HAQ and gender predict remission in early RA: experience in the Early Rheumatoid Arthritis Network (ERAN)	Insufficient reporting of duration of disease at baseline
Ma (2009)[616]	Predicting remission in trial of intensive therapy in early RA: HAQ and gender are key factors	Insufficient details reported on methods
Ma (2012)[236]	Remission in early rheumatoid arthritis: predicting treatment response	Not prediction of treatment response
Ma (2013)[617]	A multi-biomarker disease activity (Vectra™ DA algorithm) score and components are associated with sustained clinical remission in rheumatoid arthritis: the REMIRA study	Not early RA
Ma (2014)[235]	Clinical and serological predictors of remission in rheumatoid arthritis are dependent on treatment regimen	Not prediction of treatment response
Ma (2014)[618]	Multi-biomarker disease activity (Vectra® DA algorithm) score is associated with power Doppler ultrasound in patients with rheumatoid arthritis in low disease activity state: the REMIRA cohort	Not early RA
Ma (2014)[618]	Multi-biomarker disease activity (Vectra DA algorithm) score is associated with power Doppler ultrasound in patients with rheumatoid arthritis in low disease activity state: The REMIRA cohort	Not early RA

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Macchioni (2013)[619]	Ultrasonographic predictors for the development of joint damage in rheumatoid arthritis patients: a single joint prospective study	Not prediction of treatment response
Machado (2012)[620]	Predictors of rheumatoid arthritis: quantitative and semiquantitative sonographic measurements of peripheral joints	Not prediction of treatment response
Makinen (2008)[621]	Sex: a major predictor of remission as measured by 28-joint Disease Activity Score (DAS28) in early rheumatoid arthritis?	Not prediction of treatment response
Mancarella (2007)[622]	Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study	Not early RA
Manders (2013)[623]	Are TNF blocking agents associated with changes in work participation in patients with RA?	Not early RA
Manders (2014)[624]	Determinants associated with work participation in patients with established rheumatoid arthritis taking tumor necrosis factor inhibitors	Not early RA
Maneiro (2013)[625]	Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: systematic review and meta-analysis (Provisional abstract)	Not early RA
Maneiro (2013)[625]	Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: systematic review and meta-analysis	Not early RA
Maneiro (2013) [626]	Rheumatoid factor as predictor of response to non TNF antagonist biologic therapies in rheumatoid arthritis: systematic review and meta-analysis	Insufficient detail
Markusse (2013)[627]	Initial combination therapy in early rheumatoid arthritis: which patients benefit?	No relevant predictors
Marotte (2010)[628]	Biomarkers for prediction of TNFalpha blockers response in rheumatoid arthritis	Review (not systematic)
Martin (2014)[629]	Older age at rheumatoid arthritis onset and comorbidities correlate with less health assessment questionnaire-disability index and clinical disease activity index response to etanercept in the RADIUS 2 registry	Not early RA
Martin-Mola (2016)[630]	Anti-citrullinated peptide antibodies and their value for predicting responses to biologic agents: a review	Review (not systematic)
Matsushita (2016)[631]	Radiographic changes and factors associated with subsequent progression of damage in weight-bearing joints of patients with rheumatoid arthritis under TNF-blocking therapies. Three-year observational study	Not possible to obtain paper
Matteson (2004)[111]	How aggressive should initial therapy for rheumatoid arthritis be? Factors associated with response to 'non-aggressive' DMARD treatment and perspective from a 2-yr open label trial	Single-arm study (not able to assess prediction of treatment response)
Mattey (2009)[632]	Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis	Not early RA
Miceli-Richard (2006)[633]	Analysis of the shared epitope and selected pro- and anti-inflammatory cytokine genes polymorphism as predictive factors of response to adalimumab in rheumatoid arthritis patients treated in the ReAct study	No baseline disease duration reported; no relevant predictor; no relevant outcome
Mirpourian (2014)[634]	The association of body mass index with disease activity and clinical response to combination therapy in patients with rheumatoid arthritis	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Miwa (2013)[635]	Factors leading to HAQ remission after beginning biologics treatment in patients with rheumatoid arthritis	No definition of duration of RA reported and no full text identified
Miyoshi (2013)[636]	A novel method predicting good response using only background clinical data in RA patients treated with infliximab	Insufficient detail
Molina (2015)[637]	Association of socioeconomic status with treatment delays, disease activity, joint damage, and disability in rheumatoid arthritis	Not early RA
Moorthy (2007)[638]	Does smoking predict poor response to anti-TNF therapy for rheumatoid arthritis?	Not early RA
Mottonen (2002)[639]	Delay to institution of therapy and induction of remission using single drug or combination–disease-modifying antirheumatic drug therapy in early rheumatoid arthritis	No relevant outcomes
Munro (1997)[640]	C-reactive protein levels correlate with functional outcome	Not early RA
Nagasawa (2009)[641]	Improvement of the HAQ score by infliximab treatment in patients with RA: its association with disease activity and joint destruction	Not early RA
Nair (2016)[642]	A personalized approach to biological therapy using prediction of clinical response based on MRP8/14 serum complex levels in rheumatoid arthritis patients	Not early RA
Narvaez (2010)[643]	Predictors of response to rituximab in patients with active rheumatoid arthritis and inadequate response to anti-TNF agents or traditional DMARD	Not early RA
Narvaez (2011)[644]	Predictors of response to rituximab in patients with active rheumatoid arthritis and inadequate response to anti-TNF agents or traditional DMARDs	Not early RA
Navarro-Millan (2013)[645]	Predictors and persistence of new-onset clinical remission in rheumatoid arthritis patients	Not early RA
Nawata (2008)[646]	Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission	Not early RA
Nguyen (2012)[647]	The prevalence of the ultrasonographic positive power Doppler synovitis is high and predicts the risk of relapse and structural progression in rheumatoid arthritis in clinical remission: a systematic literature review and meta analysis	Not prediction of treatment response
Nguyen (2014)[648]	Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis	Not prediction of treatment response
Nishimoto (2013)[649]	Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study	Not early RA
Nishino (2015)[650]	Ultrasound evaluation of the efficacy of biologic and targeted synthetic DMARDs toward rheumatoid arthritis patients: Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort in Japan	No definition of duration of RA reported and no full text identified
Nishiyama (2013)[651]	To develop a regression model for predicting damage-related HAQ: a nationwide study based on the ninja (national database of rheumatic diseases by iR-net in Japan) 2011	Not prediction of treatment response
Nixon (2007)[652]	Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis	Insufficient detail reported

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Nordberg (2016)[653]	Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naive patients classified according to the 2010 ACR/EULAR criteria	Not prediction of treatment response
Ogawa (2015)[654]	Titre of anti-citrullinated peptide antibody affects the efficacy of first biological treatment in rheumatoid arthritis	Not early RA
Oguma (2013)[655]	(F) good outcomes at week 24 is lead by early introduction of tocilizumab and favorable treatment response up to week 12	Not early RA
Okada (2012)[656]	Characteristic of the Japanese patients with rheumatoid arthritis (RA) of rapid radiographic progression (RRP) treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) in daily practice: a large-scale prospective longitudinal cohort study (the 1st report of apple survey)	No definition of duration of RA reported and no full text identified
Okada (2013)[657]	Characteristic of the Japanese patients with rheumatoid arthritis (RA) of rapid radiographic progression (RRP) treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) in daily practice: a large-scale prospective longitudinal cohort study	No definition of duration of RA reported and no full text identified
Okada (2013)[658]	Evaluation of the Japanese patients with rheumatoid arthritis (RA) of rapid radiographic progression (RRP) treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) in daily practice: a large-scale prospective longitudinal cohort study (an interim report of Apple Survey)	No definition of duration of RA reported and no full text identified
Okada (2014)[659]	Evaluation of the Japanese patients with rheumatoid arthritis (RA) of rapid radiographic progression (RRP) treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) in daily practice: a large-scale prospective longitudinal cohort study	No definition of duration of RA reported and no full text identified
Ometto (2015)[660]	Self-reported flares predict radiographic progression in rheumatoid arthritis patients in remission undergoing etanercept tapering	Duration of disease at baseline not reported in EN abstract
Ono (2014)[661]	The impacts of disease of the joints on modified health assessment questionnaire scores in rheumatoid arthritis patients: a retrospective study using the national database of rheumatic diseases by iR-net in Japan	Not early RA
Onuora (2012)[662]	Rheumatoid arthritis: how bad is obesity for RA?	Review (not systematic)
Opris (2014)[663]	Serum drug level and anti-citrullinated peptide antibodies as biomarkers that predict EULAR response in rheumatoid arthritis-a new step to personalized medicine	Not prediction of treatment response
Opris (2015)[664]	Active synovitis in rheumatoid arthritis patients while being on SDAI remission	Not early RA
Ortiz (2014)[665]	Is there a difference in the effectiveness in the treatment of rheumatoid arthritis with rituximab in patients with rheumatoid factor positive and negative? A systematic review	Insufficient detail
Osipyants (2013)[666]	Associations between functional status and ultrasound-detected synovitis and joint damage in rheumatoid arthritis during tocilizumab treatment	Not early RA
Osipyants (2013)[667]	Imaging rather than clinical inflammation is associated with radiographic progression in tocilizumab-treated rheumatoid arthritis patients	Not early RA
Ottaviani (2015)[668]	Body mass index and response to infliximab in rheumatoid arthritis	Not early RA
Pamuk (2015)[669]	Work productivity in rheumatoid arthritis: analysis from multicenter Turkish study	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Papadopoulos (2005)[257]	Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients?	Not prediction of treatment response
Pascual-Ramos (2009)[670]	Hypervascular synovitis and American College of Rheumatology Classification Criteria as predictors of radiographic damage in early rheumatoid arthritis	Not prediction of treatment response
Pavelka (2010)[671]	Prediction of radiographic progression of rheumatoid arthritis	Language not English
Peltea (2014)[672]	Predictive factors for the EULAR response in RA patients with rituximab treatment	No definition of duration of RA and no full text identified
Peluso (2011)[673]	Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis	No relevant outcomes
Pers (2013)[674]	Multicenter retrospective study: response to tocilizumab in clinical practice is not influenced by the number of previous biotherapy or by association with a DMARD	Not early RA
Pers (2014)[675]	Predictors of response and remission in a large cohort of rheumatoid arthritis patients treated with tocilizumab in clinical practice	Not early RA
Pers (2014)[676]	TNFRII polymorphism is associated with response to TNF blockers in rheumatoid arthritis patients seronegative for ACPA	Not early RA
Pers (2015)[677]	Response to tocilizumab in rheumatoid arthritis is not influenced by the body mass index of the patient	Not early RA
Peterfy (2011)[678]	Baseline levels of the inflammatory biomarker C-reactive protein are significantly correlated with magnetic resonance imaging measures of synovitis at baseline and after 26 weeks of treatment in patients with early rheumatoid arthritis	No eligible end point
Peterfy (2012)[679]	Baseline levels of the inflammatory biomarker CRP are significantly correlated with MRI measures of synovitis at baseline and after 26 weeks of treatment in patients with early rheumatoid arthritis	No eligible end point
Plant (2000)[261]	Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis	Not prediction of treatment response
Plant (2005)[680]	What factors influence functional ability in patients with rheumatoid arthritis. Do they alter over time?	Not early RA
Pomirleanu (2013)[681]	A predictive model for remission and low disease activity in patients with established rheumatoid arthritis receiving TNF blockers	Not early RA
Pope (2011)[682]	Does C-reactive protein add value in active rheumatoid arthritis? Results from the Optimisation of Humira Trial	Not early RA
Puolakka (2004)[683]	High self-esteem is associated with low HAQ score in patients with rheumatoid arthritis	Not prediction of treatment response
Quartuccio (2009)[684]	Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis	Not early RA
Quintana-Duque (2016)[685]	Predictors of remission, erosive disease and radiographic progression in a Colombian cohort of early onset rheumatoid arthritis: a 3-year follow-up study	Not prediction of treatment response
Radovits (2007)[686]	Influence of age and gender on the interpretation of the Disease Activity Score-28 (DAS28) in rheumatoid arthritis	Disease duration at baseline not reported
Ranganath (2015)[687]	Elevated baseline power Doppler discriminates an RA subgroup highly responsive to therapy	No definition of duration of RA and no full text identified

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Rantalaiho (2015)[688]	Vitality, presenteeism, and their determinants in patients with early rheumatoid arthritis treated with a 6-month induction infliximab therapy added on a triple combination therapy	No eligible end point
Rashid (2015)[689]	Factors and reasons associated with switching in rheumatoid arthritis patients newly initiated on biologic DMARDs and impact on health care resource utilization in a managed care organization	No relevant outcomes
Rashid (2015)[690]	Factors and reasons associated with switching in rheumatoid arthritis patients experienced on biologic DMARDs and impact on health care resource utilization in an integrated healthcare system	No relevant outcomes
Rech (2015)[691]	Prediction of disease relapses by multi-biomarker disease test activity in rheumatoid arthritis patients tapering DMARD treatment	Not early RA
Reina (2013)[692]	Predictive factors of response to tocilizumab in patients with active rheumatoid arthritis	Not early RA
Rezaei (2012)[267]	In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial	Not prediction of treatment response
Rich (1999)[693]	Paucity of radiographic progression in rheumatoid arthritis treated with methotrexate as the first disease modifying antirheumatic drug	Not prediction of treatment response
Rkain (2011)[694]	Clinical and ultrasonographic assessment of evolution in patients with rheumatoid arthritis treated with tocilizumab	Not early RA
Rodrigues (2014)[695]	Obesity is a risk factor for worse treatment response in rheumatoid arthritis patients – results from reuma.pt	Not prediction of treatment response
Romao (2015)[696]	Clinical and pathological differences of elderly- and younger-onset rheumatoid arthritis in an early arthritis cohort	Insufficient detail reported on duration of RA and no full text identified
Rother (1996)[697]	Antineutrophil cytoplasmic antibodies (ANCA) in rheumatoid arthritis: a prospective study	Not early RA
Ruiz-Esquide (2011)[698]	Effects of smoking on disease activity and radiographic progression in early rheumatoid arthritis	Not prediction of treatment response
Russell (2012)[699]	Efficacy with abatacept in patients with earlier versus more longstanding disease: insights from the AIM trial	Not early RA
Saevarsdottir (2011)[74]	Development of a matrix risk model to predict rapid radiographic progression in early rheumatoid arthritis. Results from a randomized trial population	Not prediction of treatment response
Saevarsdottir (2011)[270]	Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts	Low methodological quality (overlap in treatment arms)
Saevarsdottir (2011)[700]	Predicting response to treatment in patients with rheumatoid arthritis	Not possible to obtain paper
Saevarsdottir (2011)[269]	Predictors of response to methotrexate in early DMARD naïve rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial	Not prediction of treatment response

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TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Saevarsdottir (2012)[701]	Predictive value of anti-CCP positivity on disease course and response to therapy in early rheumatoid arthritis. Results from the Swedish EIRA study	Insufficient detail on treatment response
Sagawa (2014)[702]	Long-term treatment with tocilizumab (TCZ) strongly suppresses joint destruction in biologic-naive patients with rheumatoid arthritis (RA) regardless of inflammation status	Not early RA
Sakthiswary (2014)[703]	IgA rheumatoid factor as a serological predictor of poor response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis	Not early RA
Salgado (2011)[704]	Influence of baseline rheumatoid factor on the response to tumor necrosis factor antagonists of rheumatoid arthritis patients: a systematic review and meta-analysis	Not early RA
Salgado (2013)[705]	Rheumatoid factor and response to TNF antagonists in rheumatoid arthritis: systematic review and meta-analysis of observational studies	Not early RA
Salgado (2013)[706]	Rheumatoid factor does not predict response to TNF antagonists in rheumatoid arthritis: three centers experience	Not early RA
Salgado (2013)[707]	The effect of rheumatoid factor titre on the response to TNF antagonists	Not early RA
Salgado (2014)[708]	Rheumatoid factor and response to TNF antagonists in rheumatoid arthritis: systematic review and meta-analysis of observational studies (provisional abstract)	Not early RA
Salgado (2015)[709]	Predictors of response to TNF antagonists	Review (not systematic)
Sanmartí (2003)[710]	Radiological progression in early rheumatoid arthritis after DMARDS: a one-year follow-up study in a clinical setting	Not prediction of treatment response
Sanmartí (2007)[75]	Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids	Not prediction of treatment response
Sasso (2014)[711]	The multi-biomarker disease activity score as a predictor of radiographic progression in a registry of patients with rheumatoid arthritis	Not early RA
Sauer (2015)[712]	Effectiveness and costs of biologics in veterans with rheumatoid arthritis	Disease duration at baseline not reported
Schulman (2015)[713]	High body mass index negatively impacts time to achieving sustained remission in early rheumatoid arthritis: results from a multicenter early arthritis cohort study	Insufficient details reported on assessment of prediction of treatment response
Segaud (2014)[714]	Therapeutic response to tocilizumab in rheumatoid arthritis: does body weight have an influence?	No definition of duration of RA at baseline and no full text identified
Sekiguchi (2015)[715]	Predicting factors associated with sustained clinical remission by abatacept are different between in younger and elderly patients with biologic-naive rheumatoid arthritis (ABROAD study)	Not early RA; no relevant predictive factors
Sekiguchi (2016)[716]	Differences in predictive factors for sustained clinical remission with abatacept between younger and elderly patients with biologic-naive rheumatoid arthritis: results from the ABROAD study	Not early RA
Sellam (2011)[717]	B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: a six-month, national, multicenter, open-label study	Not early RA

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Sergeant (2015)[718]	Lifestyle, clinical and psychosocial predictors of good response to methotrexate therapy in the rheumatoid arthritis medication study (RAMS)	Single-arm study (not able to assess prediction of treatment response)
Shah (2014)[719]	Serum anti-CCP antibody and its correlation with disease activity in local Pakistani rheumatoid arthritis patients	Not early RA
Sharma (2014)[720]	Biologic de-escalation in rheumatoid arthritis: cost savings and clinical success	No relevant outcomes
Shen (2010)[277]	Serum biomarkers predict progressive structural damage in the BeSt study	Not prediction of treatment response
Sherrer (1987)[721]	Disability in rheumatoid arthritis: comparison of prognostic factors across three populations	Not early RA
Shiozawa (2013)[722]	MMP-3 as a predictor that identifies a subgroup with potential radiographic progression requiring additional biologics to halt future progression among the rheumatoid arthritis patients succeedingly treated with methotrexate (MTX) alone	Not early RA
Shrestha (2013)[723]	Effect of body mass index on clinical response to anti-TNF therapies in rheumatoid arthritis: a retrospective study	No definition of duration of RA at baseline and no full text identified
Shrestha (2013)[724]	Effect of body mass index on clinical response to anti-TNF therapy in rheumatoid arthritis	No definition of duration of RA at baseline and no full text identified
Shu (2014)[725]	Impact of missing anti-cyclic citrullinated peptide (CCP) antibody serology on clinical outcomes in early rheumatoid arthritis: results from catch (Canadian early arthritis cohort)	Not prediction of treatment response
Sibilia (2012)[726]	Abatacept confers clinical efficacy regardless of baseline CRP status in patients with rheumatoid arthritis and inadequate response to methotrexate in the aim trial	Not early RA
Simone (2014)[727]	Genetic and clinical predictors of response to TNF-alpha therapy in an Italian axial-SPA cohort	Not RA
Simone (2014)[728]	Genetic and clinical predictors of response to TNF blocker in an Italian axial-SPA cohort	Not RA
Smith (2013)[729]	Can CD11C expression successfully predict response to etanercept in rheumatoid arthritis patients?	Not early RA
Smolen (2011)[730]	Baseline predictors of remission with combination etanercept-methotrexate therapy in moderately active rheumatoid arthritis: Interim results of the preserve trial	Not early RA
Smolen (2012)[731]	Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects: disassociation of the link between inflammation and destruction	Not early RA
Smolen (2015)[732]	The effect of prior disease duration and prior DMARD use on treatment outcomes in patients with early or established rheumatoid arthritis	No eligible factor
Sockalingam (2009)[733]	Prevalence of anti cyclic citrullinated peptide antibodies in Malaysian rheumatoid arthritis patients and its correlation with disease activity	Not prediction of treatment response
Soderlin (2011)[734]	Absent 'Window of Opportunity' in smokers with short disease duration. Data from BARFOT, a multicenter study of early rheumatoid arthritis	Insufficient details reported on assessment of prediction of treatment response

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Soderlin (2012)[735]	The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug	Not early RA
Soderlin (2013)[736]	Second-hand exposure to tobacco smoke and its effect on disease activity in Swedish rheumatoid arthritis patients. Data from BARFOT, a multicenter study of RA	No relevant predictors
Sokka (2000)[737]	Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores	Not early RA
Solau-Gervais (2012)[738]	Efficacy of rituximab in the treatment of rheumatoid arthritis. Influence of serological status, coprescription of methotrexate and prior TNF-alpha inhibitors exposure	Not early RA
Soliman (2011)[739]	Predictors of response to rituximab in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register (BSRBR)	Not early RA
Srirangan (2013)[740]	Functional outcome in response to treatment with DMARDs compared to anti-TNF agents in a cohort with rheumatoid arthritis	Not early RA
Stagnaro (2013)[741]	A useful mathematical model able to predict the early response to tocilizumab in rheumatoid arthritis	Insufficient detail reported
Stavropoulos-Kalinoglou (2007)[742]	Redefining overweight and obesity in rheumatoid arthritis patients	Not prediction of treatment response
Steunebrink (2015)[743]	Superiority of initial combination-over step up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: results from the DREAM registry	Disease duration at baseline not reported
Strand (2012)[744]	Factors that impact work productivity in the preserve trial: a randomized controlled trial of combination etanercept-methotrexate therapy in patients with moderately active rheumatoid arthritis	Not early RA
Strand (2013)[745]	Predictors of work impairment in a randomized controlled trial of etanercept-methotrexate therapy in patients with moderate rheumatoid arthritis	Not early RA
Strand (2015)[746]	The impact of rheumatoid arthritis on work and predictors of overall work impairment from three therapeutic scenarios	Not early RA
Sauer (2015)[712]	Effectiveness and costs of biologics in veterans with rheumatoid arthritis	Disease duration at baseline not reported
Szekanecz (2015)[747]	Analysis of the association between cigarette smoking and clinical response to certolizumab pegol treatment in Hungarian patients with rheumatoid arthritis	No baseline disease duration reported and no full text identified
Tada (2013)[748]	Predictive factors for radiographic progression in low- and standard-dose etanercept therapy for rheumatoid arthritis from the prevention of cartilage destruction by etanercept (precept) study	Not early RA
Tak (2012)[749]	A personalised medicine approach to biologic treatment of rheumatoid arthritis: a preliminary treatment algorithm	Not a prediction model or primary study
Takeuchi (2011)[750]	Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients-REACTION 52-week study	Not early RA
Takeuchi (2014)[751]	Analysis on predictors for long-term clinical efficacies of golimumab in patients with rheumatoid arthritis	Not early RA

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Takeuchi (2014)[752]	Impact of disease duration before starting adalimumab treatment on work productivity in Japanese patients with rheumatoid arthritis; analysis of 24-weeks data from the ANOUVEAU study	Not early RA
Tam (2007)[753]	Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation	Not early RA
Tamai (2012)[754]	Magnetic resonance imaging-proven osteitis at baseline predicts the early rheumatoid arthritis patients who will develop rapid radiographic progression: MRI is beneficial to find the window of opportunity in early RA	No relevant predictors
Tamai (2014)[755]	Investigation of MRI bone changes in early-stage RA patients achieved in sustained clinical good response: sub-analysis from Nagasaki University early arthritis cohort	No relevant predictors
Tanaka (2008)[756]	Efficient management of rheumatoid arthritis significantly reduces long-term functional disability	Not early RA
Tanaka (2012)[757]	Prevention of joint destruction in patients with high disease activity or high C-reactive protein	Not early RA
Tanaka (2012)[758]	Structural damages disturb functional improvement in patients with rheumatoid arthritis treated with etanercept	Not early RA
Tanaka (2013)[759]	Efficacy and safety of tocilizumab therapy in rheumatoid arthritis: prevalence and predictive factors of sustained remission	Not early RA
Tanaka (2015)[760]	A longitudinal study of factors contributing to the worsening of absenteeism in patients with rheumatoid arthritis based on the IORRA cohort	Not early RA
Tanaka (2016)[761]	Prevention of joint destruction in patients with high disease activity or high C-reactive protein levels: post hoc analysis of the GO-FORTH study	Not possible to obtain paper
Teitsma (2015)[762]	Predicting the need for additional treatment in early rheumatoid arthritis patients treated to target on methotrexate monotherapy	Insufficient details reported on assessment of prediction of treatment response
Terao (2015)[763]	Rheumatoid factor is associated with the distribution of hand joint destruction in rheumatoid arthritis	Not early RA
Thorne (2014)[764]	Effectiveness and safety of infliximab in rheumatoid arthritis: analysis from a Canadian multicenter prospective observational registry	Not early RA
Tolusso (2010)[765]	Analysis of the association of CDA (cytidin deaminase) (K27Q), TNF-(–308G>A) and PTPN22 R620W genetic polymorphisms with auto-antibody seropositive RA and the response to B cell depletion	No baseline disease duration reported (Also no relevant predictors)
Tony (2011)[766]	Predictive factors for response to rituximab in patients with rheumatoid arthritis (FIRST)	Not possible to obtain paper
Torrente-Segarra (2014)[767]	Assessment of 12-month efficacy and safety of 168 certolizumab pegol rheumatoid arthritis treated patients from a multicenter retrospective national study in Spain	Not early RA
Torrente-Segarra (2016)[768]	RENACER study: assessment of 12-month efficacy and safety of 168 certolizumab PEGol rheumatoid arthritis-treated patients from a Spanish multicenter national database	Not early RA
Troelsen (2012)[769]	IgG glycosylation changes and MBL2 polymorphisms: associations with markers of systemic inflammation and joint destruction in rheumatoid arthritis	Not early RA

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Tsuji (2014)[770]	Baseline procalcitonin (PCT) level as a predictive marker for clinical remission (DAS28-ESR, CDAI) at 52 weeks in biologic naive rheumatoid arthritis (RA) patients treated by tocilizumab (TCZ); a single centre retrospective study	Disease duration at baseline not reported
Ursum (2010)[771]	Levels of anti-citrullinated protein antibodies and IgM rheumatoid factor are not associated with outcome in early arthritis patients: a cohort study	Not early RA
van den Broek (2012)[772]	The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study	Not prediction of treatment response
van den Broek (2013)[773]	Personalized medicine: predicting responses to therapy in patients with RA	Review (not systematic)
van der Heijde (2005)[774]	Baseline CRP concentrations predict radiographic progression in MTX-naive patients with recent-onset RA: subanalysis of the PREMIER study [abstract]	Not prediction of treatment response
van der Helm-van Mil (2005)[296]	Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis	Not prediction of treatment response
van der Helm-van Mil (2008)[775]	A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis	Not prediction of treatment response
van Der Horst-Bruinsma (2011)[776]	Inclusion criteria based on DAS28 score: strength of improvement is less dependent on baseline disease activity than expected	Commentary (not a study)
van der Maas (2014)[777]	Validity of OMERACT preliminary flare questions in a randomized controlled trial, that assesses impact of disease activity guided down-titration of anti-TNF treatment in rheumatoid arthritis patients in low disease activity	Not early RA
van der Woude (2009)[778]	Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts	No relevant outcome
van Gaalen (2004)[779]	Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis	Insufficient information on treatment response
van Jaarsveld (1999)[300]	The prognostic value of the antiperinuclear factor, anti-citrullinated peptide antibodies and rheumatoid factor in early rheumatoid arthritis	Not prediction of treatment response
van Laar (2007)[780]	Do high levels of IgA rheumatoid factor indicate a poor response to treatment with TNF inhibitors in patients with RA?	Commentary
van Nies (2014)[781]	What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review	Review – cross-checked
van Sijl (2013)[782]	A novel and effective prediction model of response to rituximab in rheumatoid arthritis	Insufficient detail reported
van Vollenhoven (2009)[783]	Six-month results from the collaborative European registries for rituximab in rheumatoid arthritis (CERERRA). Efficacy of rituximab is highest in RF-positive patients and in those who failed at most one prior anti-TNF	Not early RA
van Vollenhoven (2014)[784]	A prediction model that identifies patients most likely to benefit from first-line therapy with adalimumab plus methotrexate in early rheumatoid arthritis	Insufficient detail reported
Vastesaeger (2009)[78]	Matrix risk model for prediction of rapid radiographic progression in rheumatoid arthritis	Not prediction of treatment response

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Vastesaeger (2016)[785]	Prediction of remission and low disease activity in disease-modifying anti-rheumatic drug-refractory patients with rheumatoid arthritis treated with golimumab	Not early RA
Vazquez (2007)[786]	Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting	Not prediction of treatment response
Velloso Feijoo (2013)[787]	B cell depletion therapy in a cohort of patients with seropositive and seronegative rheumatoid arthritis	Not early RA
Ven (2014)[788]	Can we use ultrasound to identify rheumatoid arthritis patients in remission who can taper their medication?	Disease duration at baseline not reported
Verschueren (2009)[789]	Predictors of remission, normalized physical function, and changes in the working situation during follow-up of patients with early rheumatoid arthritis: an observational study	Not prediction of treatment response
Verstappen (2005)[790]	Working status among Dutch patients with rheumatoid arthritis: work disability and working conditions	Not early RA
Verstappen (2009)[791]	Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate (the CAMERA study)	No relevant outcomes
Verstappen (2010)[792]	Working status in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: results from the British Society for Rheumatology Biologics Register	Not early RA
Vesperini (2013)[307]	Association of tobacco exposure and reduction of radiographic progression in early rheumatoid arthritis: results from a French multicenter cohort	Not prediction of treatment response
Vidal (2014)[793]	Influence of body mass index on disease activity and radiographic joint damage in rheumatoid arthritis: a systematic review and meta-analysis	Not early RA
Visman (2011)[794]	Effect of the application of trial inclusion criteria on the efficacy of adalimumab therapy in a rheumatoid arthritis cohort	Not early RA
Visser (2008)[795]	Pretreatment serum levels of anti-cyclic citrullinated peptide antibodies are associated with the response to methotrexate in recent-onset arthritis	Population (UA)
Visser (2010)[79]	A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study	Not prediction of treatment response
Visvanathan (2007)[311]	Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis	No relevant predictors
Vital (2010)[796]	Serum cytokine profile predicts response to rituximab therapy in rheumatoid arthritis	Not prediction of treatment response
Volkov (2013)[797]	Monitoring anti-interleukin 6 receptor antibody treatment in rheumatoid arthritis and prediction progressive structural damage of the wrist joints by ultrasonography	Not early RA
Vreju (2016)[798]	Subclinical ultrasound synovitis in a particular joint is associated with ultrasound evidence of bone erosions in that same joint in rheumatoid patients in clinical remission	Not early RA
Wagner (2009)[799]	Serum markers associated with clinical response in methotrexate naïve rheumatoid arthritis patients treated with golimumab, a human anti-TNFα monoclonal antibody	Not possible to obtain paper

continued

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Wagner (2010)[800]	Association of serum markers with clinical response measures in rheumatoid arthritis patients treated with golimumab, a human anti-TNF alpha monoclonal antibody	Not possible to obtain paper
Wang (2016)[801]	Short-term efficacy reliably predicts long-term clinical benefit in rheumatoid arthritis clinical trials as demonstrated by model-based meta-analysis	No relevant outcomes
Wang (2016)[802]	Relationship between baseline and early changes in C-reactive protein and interleukin-6 levels and clinical response to tocilizumab in rheumatoid arthritis	Not early RA
Watanabe (2013)[803]	Tocilizumab efficiently halts radiographic progression in patients with rheumatoid arthritis and swollen joint counts within a year predict long-term radiographic outcomes: three year results from Michinoku Tocilizumab Study Group	Not early RA
Weinblatt (2006)[804]	Predictors of poor radiographic response in rheumatoid arthritis subjects treated with methotrexate: preliminary analysis from the era and tempo studies	Not prediction of treatment response
Weinblatt (2011)[805]	Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate	Not early RA
Wessels (2007)[312]	A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis	Not prediction of treatment response
Westhoff (2013)[806]	Indicators of depression are stronger predictors of work disability in early arthritis than disease activity or response to therapy	No relevant outcomes
Wevers-De Boer (2011)[807]	Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis	Treatment duration of < 6 months
Wevers-De Boer (2012)[808]	Extended report: remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study)	Treatment duration of < 6 months
Wevers-De Boer (2012)[809]	Remission after one year in ACPA positive and ACPA negative patients with early arthritis	Treatment duration of < 6 months
Wevers-De Boer (2013)[810]	Early metacarpal bone mineral density loss is predictive for radiologic joint damage progression after 1 year in patients with early arthritis	Combined sample of RA and UA, analyses not reported separately in this abstract
White (2009)[811]	Clinical features of disease severity and body mass index predict outcome at 6 months in a cohort of patients with early rheumatoid arthritis	Insufficient detail reported on methods and treatment
Wolfe (2000)[318]	The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis	Not early RA
Wolfe (2012)[812]	Effect of body mass index on mortality and clinical status in rheumatoid arthritis	Not early RA
Xibille (2013)[813]	Plasma adiponectin level and body mass index (BMI) predict response to treatment in patients with rheumatoid arthritis	Not early RA
Xibille (2013)[814]	Leptin and adiponectin serum levels as predictors of treatment response in patients with rheumatoid arthritis	Not early RA
Yamanaka (2007)[815]	Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM)	Not early RA
Yamanaka (2015)[816]	Trend of patient characteristics and its impact on the response to adalimumab in patients with rheumatoid arthritis: post hoc time-course analysis of an all-case pms in Japan	Not possible to obtain paper
Yamasaki (2014)[817]	Predictive marker for the long-term discontinuation of infliximab in rheumatoid arthritis with clinical remission	Disease duration at baseline not reported

TABLE 33 Review 2 excluded studies with rationale (*continued*)

First author (date)	Title	Justification for exclusion
Yazici (2011)[818]	Greater remission rates in patients with early versus long-standing disease in biologic-naive rheumatoid arthritis patients treated with abatacept: a post hoc analysis of randomized clinical trial data	Not early RA
Yoshida (2015)[819]	Incidence and predictors of biological antirheumatic drug discontinuation attempts among patients with rheumatoid arthritis in remission: a CORRONA and NinJa collaborative cohort study	Not early RA
Yoshimi (2013)[820]	Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis	Not early RA
Yuasa (2013)[821]	Treatment responses and their predictors in patients with rheumatoid arthritis treated with biological agents	Not early RA
Zeidler (2012)[822]	Reply to: very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study	No data (comment)
Zhang (2009)[823]	The sensitivity to change for lower disease activity is greater than for higher disease activity in rheumatoid arthritis trials	No relevant outcomes
Zheng (2014)[824]	Application of high frequency color Doppler ultrasound in the monitoring of rheumatoid arthritis treatment	Not early RA
Zhilyaev (2014)[825]	Efficacy of biological treatment in cohort of rheumatoid arthritis patients in Moscow	Not early RA
Zufferey (2013)[826]	Disease activity in rheumatoid arthritis patients at initiation of biologic agents and 1 year of treatment: results from the Swiss SCQM registry	Not early RA

UA, undifferentiated arthritis.

Appendix 9 Additional evidence tables: review 2

TABLE 34 Additional population characteristics of included primary studies at baseline

Author (year), name of trial or cohort (if relevant)	Characteristic											
	Group/ treatment arm	Mean/median age (years)	Sex (% female)	Mean/median HAQ score at baseline	Mean/median baseline erosions on radiograph or percentage of erosions	ACPA +/anti-CCP-positive at baseline (%)	RF positive at baseline (%)	Mean/median SJC at baseline	Mean/median ESR at baseline	Mean/median CRP levels at baseline	Baseline smoking status	Vascularity of synovium using PD ultrasound
Garnero (2002)[102]	All participants	49 (SD 12)	80	1.49 (SD 0.67)	SHS erosion score: 6.3 (SD 9.5) SHS total score: 11.9 (SD 16.6)	NR	88	23 (SD 11)	NR	4.2 mg/dl (SD 6.0)	NR	NR
Heimans (2013)[103] BeSt	All participants	55 (SD 14)[a]	68[a]	1.4 (SD 0.7)[a]	SHS erosion score: 3.7 (SD 5.1) SHS total score: 6.6 (SD 8.2)	57[a]	65[a]	NR	NR	NR	Smoker, *n*: 177 (35%)[a]	NR
	BMI of < 25 kg/m^2	53 (SD 15)	72	1.4 (SD 0.6)	NR	65	69	13 (IQR 10–19)	38 mm/hour (IQR 20–58 mm/hour)	20 mg/l (IQR 8–55 mg/l)	Smoker, *n*: 88 (41%)	NR
	BMI of ≥ 25 kg/m^2	56 (SD 13)	64	1.4 (SD 0.7)	NR	59	62	14 (IQR 9–18)	34 mm/hour (IQR 18–56 mm/hour)	21 mg/l (IQR 9–50 mg/l)	Smoker, *n*: 89 (31%)	NR
	Sequential monotherapy	54 (SD 13)	68	1.4 (SD 0.7)[b]	SHS erosion score: 4.1 (SD 6.2) SHS total score: 7.3 (SD 9.5)	NR	67	NR	NR	NR	NR	NR
	Step-up combination therapy	54 (SD 13)	71	1.4 (SD 0.6)[b]	SHS erosion score: 3.5 (SD 4.3) SHS total score: 6.3 (SD 6.9)	NR	64	NR	NR	NR	NR	NR
	MTX and SSZ and tapered prednisone	55 (SD 14)	65	1.4 (SD 0.7)[b]	SHS erosion score: 3.3 (SD 4.3) SHS total score: 5.9 (SD 6.5)	NR	65	NR	NR	NR	NR	NR
	MTX and IFX	54 (SD 14)	66	1.4 (SD 0.7)[b]	SHS erosion score: 3.9 (SD 5.8) SHS total score: 7.0 (SD 10.0)	NR	64	NR	NR	NR	NR	NR

Author (year), name of trial or cohort (if relevant)	Characteristic											
	Group/ treatment arm	Mean/median age (years)	Sex (% female)	Mean/median HAQ score at baseline	Mean/median baseline erosions on radiograph or percentage of erosions	ACPA +/anti-CCP-positive at baseline (%)	RF positive at baseline (%)	Mean/median SJC at baseline	Mean/median ESR at baseline	Mean/median CRP levels at baseline	Baseline smoking status	Vascularity of synovium using PD ultrasound
Huizinga (2015)[104] AVERT	All participants	47.0 (SD 12.6)[c]	77.8	1.4 (SD 0.66)	NR	58	95.2[c]	NR	NR	17.5 mg/l (SD 25.0 mg/l)[c]	NR	NR
	ABT s.c. and MTX	46.4 (SD 13.2)[c]	79.8[c]	1.5 (SD 0.68)[c]	NR	56	95[c]	NR	NR	18.1 mg/l (SD 28.4 mg/l)[c]	NR	NR
	ABT s.c.	45.4 (SD 11.9)[c]	76.7[c]	1.4 (SD 0.66)[c]	NR	55	95.7[c]	NR	NR	16.9 mg/l (SD 23.9 mg/l)[c]	NR	NR
	MTX	49.1 (SD 12.4)[c]	76.7[c]	1.4 (SD 0.65)[c]	NR	64	94.8[c]	NR	NR	17.3 mg/l (SD 22.4 mg/l)[c]	NR	NR
Maska (2012)[105] TEAR	All participants (with serum cotinine at baseline and week 48)	49.6 (SD 12.2)	73	1.2 (SD 0.4)	NR	NR	NR	12.5 (SD 5.7)	32.8 mm/hour (SD 24.0 mm/ hour)	NR	See below	NR
	Current smokers	50.1 (SD 10.8)	67	1.3 (SD 0.4)	NR	NR	NR	12.5 (SD 5.8)	32.6 mm/hour (SD 24.3 mm/ hour)	NR	Current smokers: 119 (29%)	NR
	Non-smokers	49.4 (SD 12.7)	75	1.2 (SD 0.4)	NR	NR	NR	12.4 (SD 5.7)	32.9 mm/hour (SD 23.9 mm/ hour)	NR	Non-smokers: 293 (71%)	NR
Mustila (2011)[106] FIN-RACo	All participants	47 (SD 10)[a]	63[a]	0.87 (SD 0.58)[a]	Erosive disease: 45%[a]	71[a]	65[a]	13 (SD 7)[a]	37 mm/hour (SD 23 mm/hour)[a]	NR	NR	NR
	ACPA+	NR	NR	NR	Erosive disease: 54%	100	83	NR	NR	NR	NR	NR
	ACPA–	NR	NR	NR	Erosive disease: 22%	0	22	NR	NR	NR	NR	NR
	MTX and HCQ and SSZ in a TTT regime	46 (SD 10)	61	0.84 (SD 0.54)	Erosions in hand or foot radiographs: 42%	NR	68	13 (SD 6)	37 mm/hour (SD 24 mm/hour)	NR	NR	NR
	cDMARD sequential monotherapy in a TTT regime (starting with SSZ)	48 (SD 11)	65	0.91 (SD 0.63)	Erosions in hand or foot radiographs: 48%	NR	62	14 (SD 7)	37 mm/hour (SD 21 mm/hour)	NR	NR	NR

continued

TABLE 34 Additional population characteristics of included primary studies at baseline (*continued*)

Author (year), name of trial or cohort (if relevant)	Characteristic											
	Group/ treatment arm	Mean/median age (years)	Sex (% female)	Mean/median HAQ score at baseline	Mean/median baseline erosions on radiograph or percentage of erosions	ACPA +/anti-CCP-positive at baseline (%)	RF positive at baseline (%)	Mean/median SJC at baseline	Mean/median ESR at baseline	Mean/median CRP levels at baseline	Baseline smoking status	Vascularity of synovium using PD ultrasound
Pasero (1996)[107]	All participants	49.6 (SD 11.6)[a]	78	NR	Number of patients with erosions: 193[a] Number of patients without erosions: 91[a]	NR	NR	14.8 (SD 7.7)[a]	47.2 mm/hour (SD 28.0 mm/ hour)[a]	8.4 mg/dl (SD 17.1 mg/dl)	NR	NR
	Patients with joint erosions at baseline	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Patients without joint erosions at baseline	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CsA arm	48.4 (SD 11.6)	77	NR	Number of patients with erosions: 104 Number of patients without erosions: 37	NR	NR	14.9 (SD 7.5)	46.9 mm/hour (SD 25.2 mm/ hour)	8.3 mg/dl (SD 16.7 mg/dl)	NR	NR
	Other cDMARDs arm	50.8 (SD 11.5)	78	NR	Number of patients with erosions: 89 Number of patients without erosions: 54	NR	NR	14.7 (SD 7.8)	47.5 mm/hour (SD 30.8 mm/ hour)	8.5 mg/dl (SD 17.5 mg/dl)	NR	NR
Rau (1998)[108]	All participants	55.5 (SD 9.5)[a]	66	NR	Mean radiographic score (0–190): 5.2[a] Number of eroded joints (0–38): 4.4[a]	NR	61	15.2 (SD 6.9)[a]	40.9 mm/hour (SD 24.0 mm/ hour)[a]	4.4 mg/dl (SD 4.0 mg/dl)[a]	NR	NR
	MTX	54.2 (SD 8.6)	60	NR	Mean radiographic score (0–190): 5.8 Number of eroded joints (0–38): 4.2	NR	68	15.3 (± 6.6)	41.1 mm/hour (± 24.5 mm/ hour)	4.1 mg/100 ml (± 3.6 mg/ 100 ml)	NR	NR
	GSTM	56.8 (SD 10.4)	72	NR	Mean radiographic score (0–190): 4.6 Number of eroded joints (0–38): 4.6	NR	54	15.1 (± 7.2)	40.6 mm/hour (± 23.6 mm/ hour)	4.6 mg/100 ml (± 4.4 mg/ 100 ml)	NR	NR

Author (year), name of trial or cohort (if relevant)	Characteristic											
	Group/ treatment arm	Mean/median age (years)	Sex (% female)	Mean/median HAQ score at baseline	Mean/median baseline erosions on radiograph or percentage of erosions	ACPA +/anti-CCP-positive at baseline (%)	RF positive at baseline (%)	Mean/median SJC at baseline	Mean/median ESR at baseline	Mean/median CRP levels at baseline	Baseline smoking status	Vascularity of synovium using PD ultrasound
Seegobin (2014)[109]	All participants	54 (IQR 20–89)[a,d]	69	1.6 (SD 0.7)	NR	48	68	NR	NR	NR	NR	NR
CARDERA	ACPA+	54.0 (IQR 46.0–64.0)	67	1.62 (IQR 1.00–2.12)	Larsen score: 7.50 (IQR 2.50–21.25)	100	79[e]	NR	NR	NR	NR	NR
	ACPA–	55.0 (IQR 47.0–62.0)	74	1.62 (IQR 1.12–2.12)	Larsen score: 4.50 (IQR 1.00–9.50)	0	39	NR	NR	NR	NR	NR
	MTX monotherapy	54 (range 21–80)[d,f]	67[f]	1.5 (SD 0.7)[f]	Larsen score: 7 (IQR 3–15)[f]	NR	66[f]	NR	NR	NR	NR	NR
	CsA and MTX	53 (range 20–89)[d,f]	66[f]	1.7 (SD 0.7)[f]	Larsen score: 8 (IQR 3–23)[f]	NR	65[f]	NR	NR	NR	NR	NR
	Prednisolone and MTX	54 (range 27–84)[d,f]	66[f]	1.6 (0.7)[f]	Larsen score: 6 (IQR 2–20)[f]	NR	66[f]	NR	NR	NR	NR	NR
	Triple therapy	55 (range 20–78)[d,f]	67[f]	1.6 (SD 0.7)	Larsen score: 5 (IQR 2–14)[f]	NR	72[f]	NR	NR	NR	NR	NR
Smolen (2006)[100]	All participants	50 (SD 13)[a]	71	1.5 (SD 0.6)	82.5% with erosions[a]	NR	72[a]	22 (SD 10)[a]	44 mm/hour (SD 28 mm/hour)[a]	3.0 mg/dl (SD 3.1 mg/dl)[a]	NR	NR
Vastesaeger (2009)[78]	MTX	50 (SD 13)	75	1.5 (SD 0.6)[a]	80% with erosions	NR	71	22 (SD 11)	43 mm/hour (SD 28 mm/hour)	2.6 mg/dl (SD 2.9 mg/dl)	NR	NR
ASPIRE	IFX (all doses)	50 (SD 13)[a]	70	1.5 (SD 0.6)	83.5% with erosions[a]	NR	72[a]	22 (SD 10)[a]	44 mm/hour (SD 28 mm/hour)[a]	3.0 mg/dl (SD 3.3 mg/dl)[a]	NR	NR
	MTX and IFX 3 mg/kg	51 (SD 12)	71	1.5 (SD 0.7)[a]	84% with erosions	NR	71	21 (SD 10)	45 mm/hour (SD 29 mm/hour)	2.9 mg/dl (SD 3.3 mg/dl)	NR	NR
	MTX and IFX 6 mg/kg	50 (SD 13)	68	1.5 (SD 0.6)	83% with erosions	NR	73	22 (SD 11)	44 mm/hour (SD 27 mm/hour)	3.0 mg/l (SD 3.4 mg/dl)	NR	NR

continued

TABLE 34 Additional population characteristics of included primary studies at baseline (*continued*)

Author (year), name of trial or cohort (if relevant)	Characteristic											
	Group/ treatment arm	Mean/median age (years)	Sex (% female)	Mean/median HAQ score at baseline	Mean/median baseline erosions on radiograph or percentage of erosions	ACPA +/anti-CCP-positive at baseline (%)	RF positive at baseline (%)	Mean/median SJC at baseline	Mean/median ESR at baseline	Mean/median CRP levels at baseline	Baseline smoking status	Vascularity of synovium using PD ultrasound
Sokolove (2015)[110]	All patients	NR	NR	NR	NR	76	NR	NR	NR	NR	NR	NR
AMPLE	Anti-CCP2 negative	ABT: 52 (IQR 24.0–80.0) ADA: 58 (IQR 21.0–83.0)	ABT: 84.8 ADA: 85.2	ABT: 1.3 (IQR 0.0–2.9) ADA: 1.4 (IQR 0.0–2.6)	NR	0	ABT: 42.4 ADA: 51.9	NR	NR	ABT: 0.6 mg/dl (IQR 0.0–10.4 mg/dl) ADA: 0.6 mg/dl (IQR 0.0–42 mg/dl)	ABT: • Never: 52% • Past: 21% • Current: 27% ADA: • Never: 57% • Past: 30% • Current: 13%	NR
	Anti-CCP2 positive; Q1	ABT: 50 (IQR 22.0–70.0) ADA: 50 (IQR 19.0–78.0)	ABT: 88.1 ADA: 83.6	ABT: 1.4 (IQR 0.0–2.5) ADA: 1.3 (IQR 0.0–2.5)	NR	100	ABT: 85.7 ADA: 92.7	NR	NR	ABT: 0.8 mg/dl (IQR 0.1–8.4 mg/dl) ADA: 0.6 mg/dl (IQR 0.0–4.8 mg/dl)	ABT: • Never: 64% • Past: 14% • Current: 21% ADA: • Never: 55% • Past: 20% • Current: 26%	NR
	Anti-CCP2 positive; Q2	ABT: 52 (IQR 21.0–78.0) ADA: 49 (IQR 22.0–73.0)	ABT: 80.4 ADA: 87.0	ABT: 1.7 (IQR 0.0–2.8) ADA: 1.6 (IQR 0.0–2.9)	NR	100	ABT: 98.0 ADA: 93.5	NR	NR	ABT: 0.9 mg/dl (IQR 0.0–9.4 mg/dl) ADA: 1.3 mg/dl (IQR 0.1–5.8 mg/dl)	ABT: • Never: 53% • Past: 16% • Current: 31% ADA: • Never: 59% • Past: 20% • Current: 22%	NR

Author (year), name of trial or cohort (if relevant)	Characteristic											
	Group/ treatment arm	Mean/median age (years)	Sex (% female)	Mean/median HAQ score at baseline	Mean/median baseline erosions on radiograph or percentage of erosions	ACPA +/anti-CCP-positive at baseline (%)	RF positive at baseline (%)	Mean/median SJC at baseline	Mean/median ESR at baseline	Mean/median CRP levels at baseline	Baseline smoking status	Vascularity of synovium using PD ultrasound
	Anti-CCP2 positive; Q3	ABT: 47.5 (IQR 25.0–73.0) ADA: 52 (IQR 26.0–78.0)	ABT: 82.6 ADA: 80.4	ABT: 1.4 (IQR 0.0–2.8) ADA: 1.6 (IQR 0.0–3.0)	NR	100	ABT: 100.0 ADA: 96.1	NR	NR	ABT: 0.9 mg/dl (IQR 0.1–11.3 mg/dl) ADA: 1.0 mg/dl (IQR 0.0–9.0 mg/dl)	ABT: • Never: 57% • Past: 11% • Current: 33% ADA: • Never: 57% • Past: 18% • Current: 26%	NR
	Anti-CCP2 positive; Q4	ABT: 51.5 (IQR 19.0–70.0) ADA: 52 (IQR 27.0–85.0)	ABT: 78.3 ADA: 72.5	ABT: 1.6 (IQR 0.0–2.9) ADA: 1.8 (IQR 0.0–2.8)	NR	100	ABT: 95.7 ADA: 100.0	NR	NR	ABT: 0.9 mg/dl (IQR 0.0–13.9 mg/dl) ADA: 0.7 mg/dl (IQR 0.0–11.8 mg/dl)	ABT: • Never: 41% • Past: 35% • Current: 24% ADA: • Never: 57% • Past: 16% • Current: 28%	NR
Taylor (2004)[101]	All	53.3 (SD 12.9)[a]	75[a]	NR	Total SHS: 8.1 (11.8)[a]	NR	NR	9.2 (SD 3.2)[a]	31.6 mm/hour (SD 20.3 mm/hour)[a]	18.9 mg/dl (SD 23.0 mg/dl)[a]	NR	Total CDA: 8597 pixels (SD 6644)[a]
	MTX	51.4 (SD 14.0)	67[a]	NR	Total SHS: 7.1 (7.8)	NR	NR	8.8 (SD 2.7)	35.7 mm/hour (SD 21.2)	25.0 mg/dl (SD 25.4 mg/dl)	NR	Total CDA: 8212 pixels (SD 6479)
	IFX and MTX	55.2 (SD 11.8)	83[a]	NR	Total SHS: 9.0 (15.9)	NR	NR	9.5 (SD 3.8)	27.4 mm/hour (SD 19.5 mm/hour)	12.7 mg/dl (SD 20.7 mg/dl)	NR	Total CDA: 9072 pixels (SD 6718)

ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; AMPLE, abatacept vs. adalimumab in biologic naive RA patients with background MTX; anti-CCP2, anti-cyclic citrullinated peptide-2; AVERT, Assessing Very Early Rheumatoid arthritis Treatment; CARDERA, Combination Anti-Rheumatic Drugs in Early RA; CDA, colour Doppler area; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; NR, not reported; PD, power Doppler; Q1/Q2/Q3/Q4, quartile 1/quartile 2/quartile 3/quartile 4; s.c., subcutaneous administration; TEAR, Treatment of Early Aggressive Rheumatoid arthritis.

a Calculated.
b D-HAQ (Dutch version of the Health Assessment Questionnaire).
c From Emery *et al.* (2015).[116]
d Mean (range).
e $p < 0.001$ vs. ACPA–.
f From Choy *et al.* (2008).[114]

Appendix 10 Interaction between baseline predictor and treatment figures

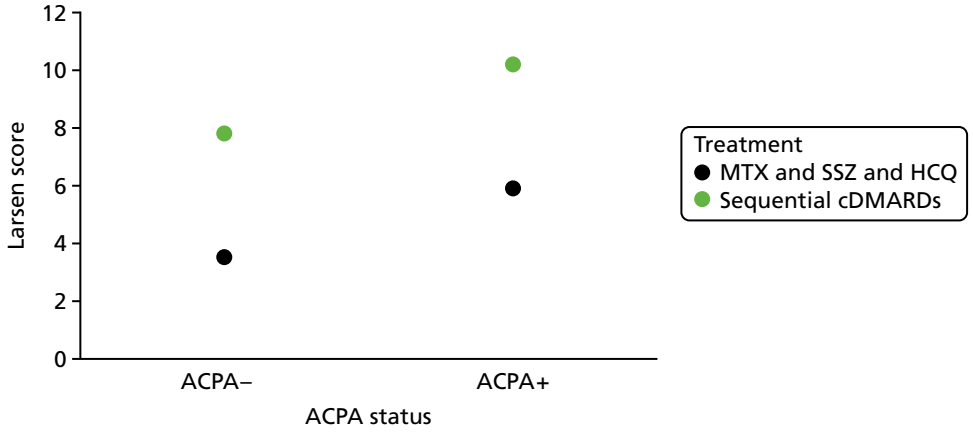

FIGURE 10 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 1 year from Mustila *et al.*[106] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

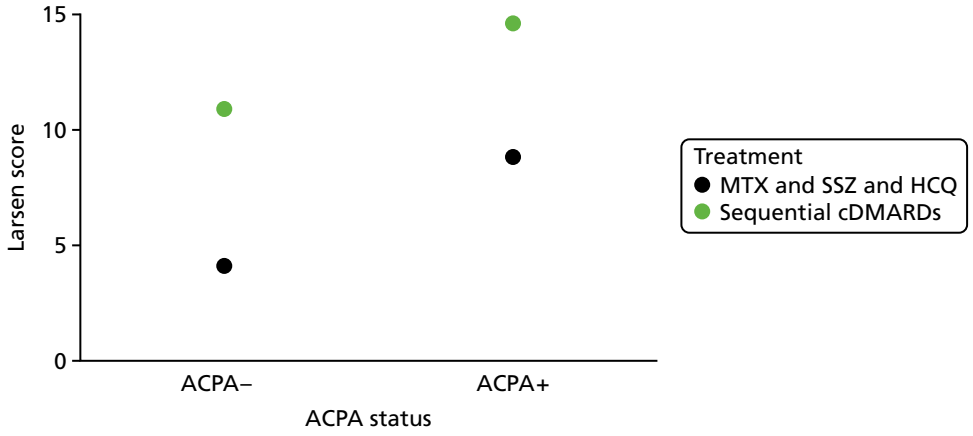

FIGURE 11 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 2 years from Mustila *et al.*[106] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

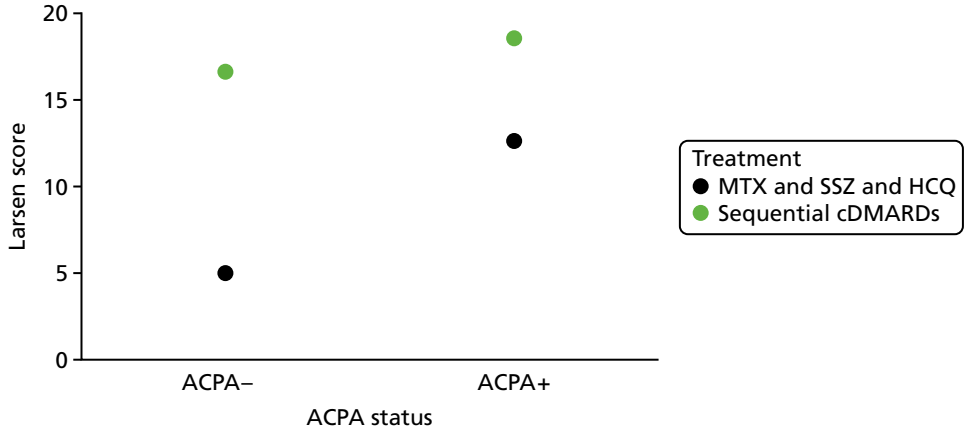

FIGURE 12 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 3 years from Mustila *et al.*[106] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

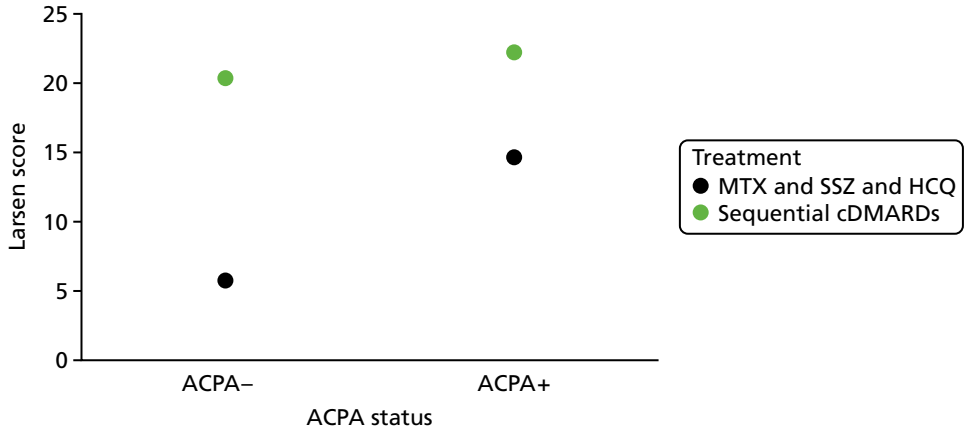

FIGURE 13 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 4 years from Mustila *et al.*[106] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

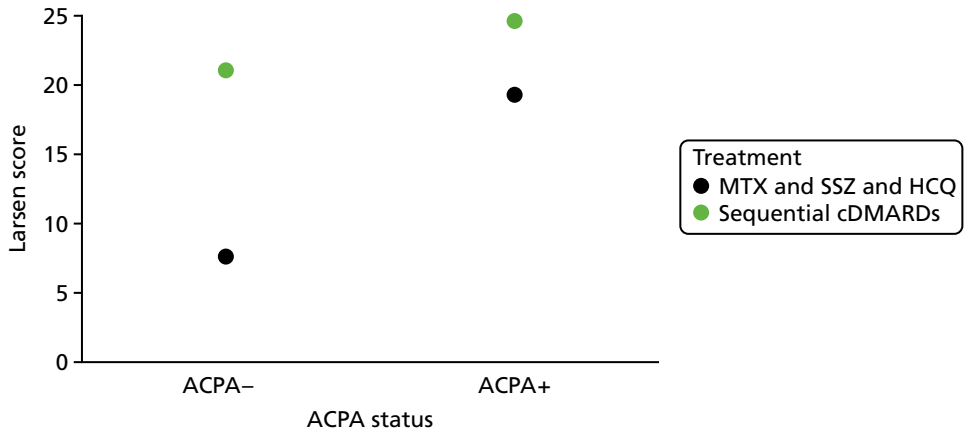

FIGURE 14 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 5 years from Mustila *et al.*[106] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

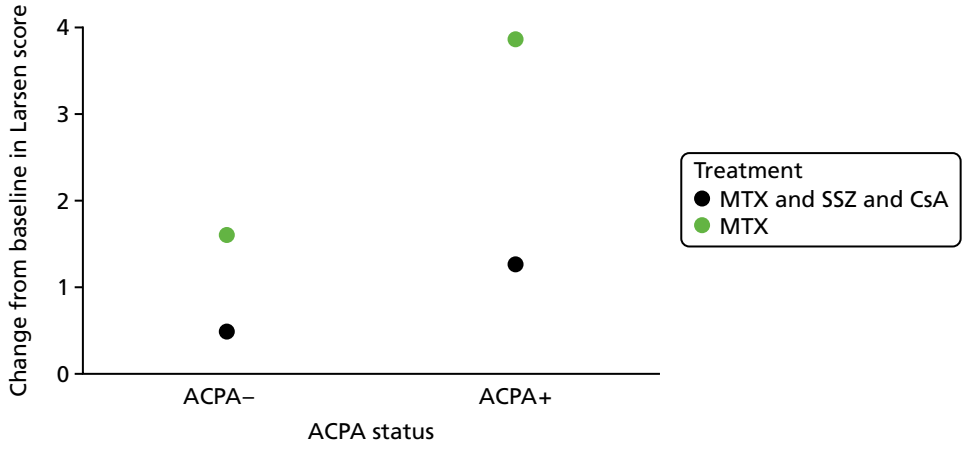

FIGURE 15 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 6 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

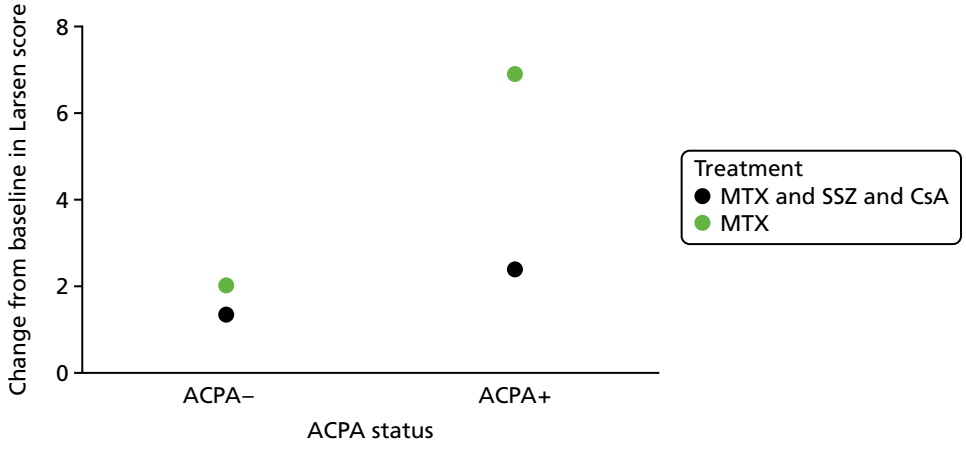

FIGURE 16 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 12 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

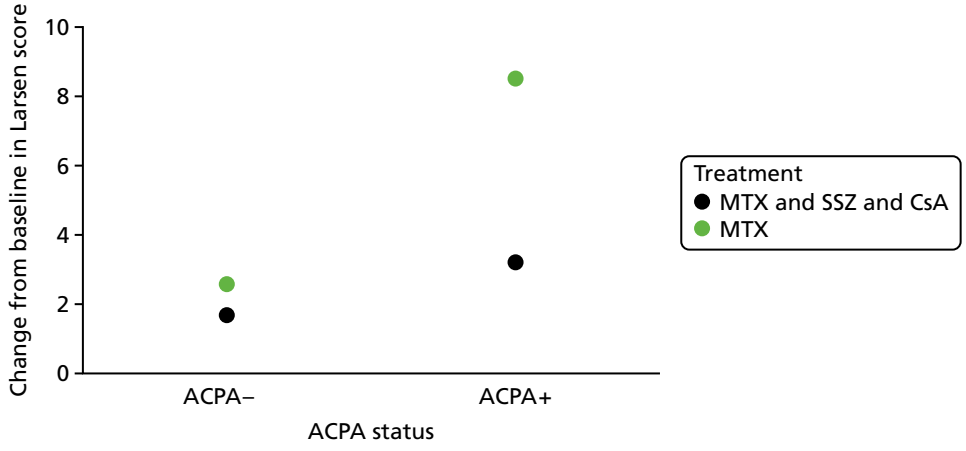

FIGURE 17 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 18 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

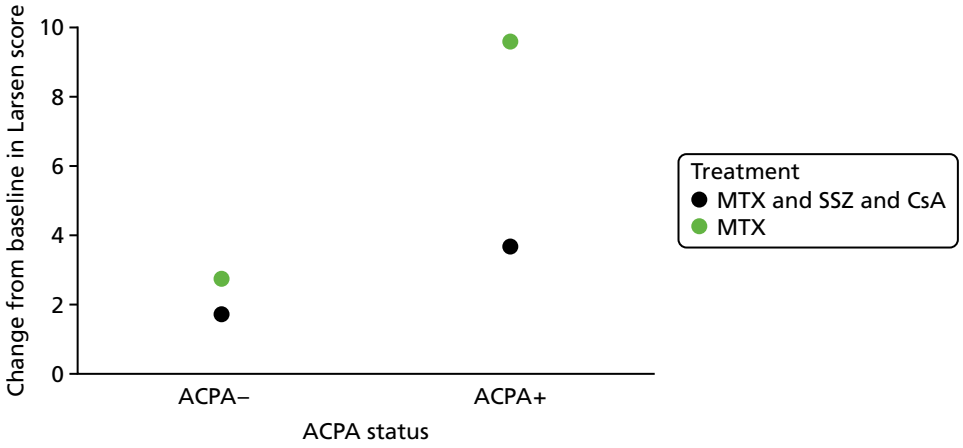

FIGURE 18 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 24 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

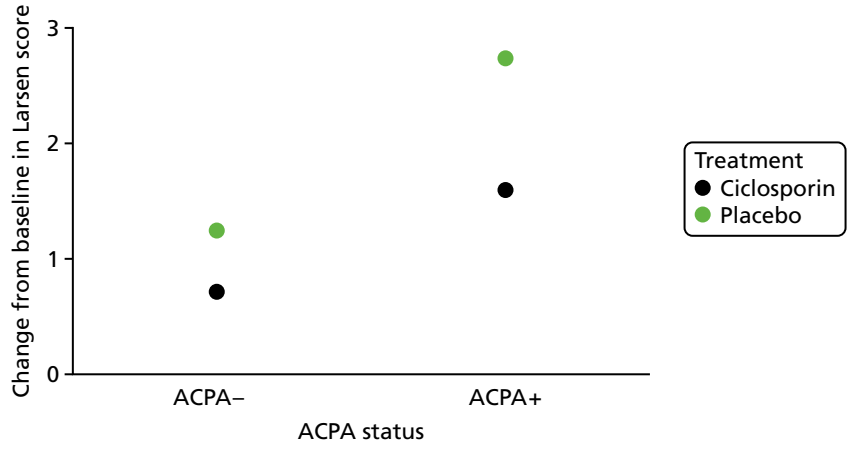

FIGURE 19 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 6 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

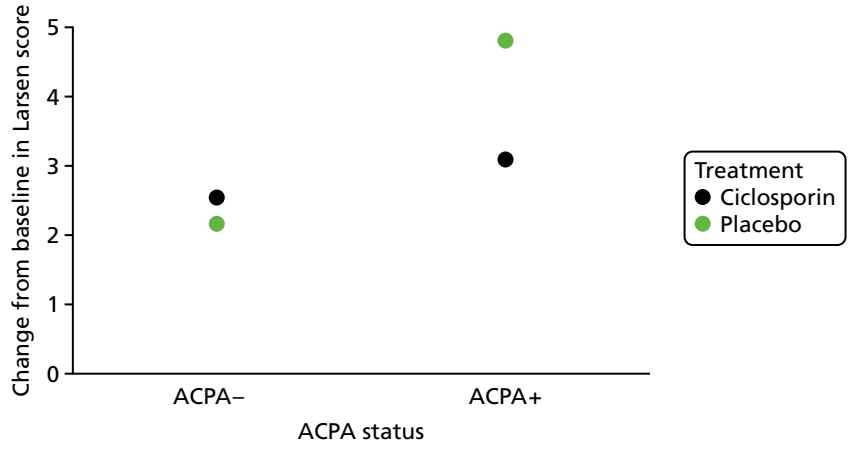

FIGURE 20 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 12 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

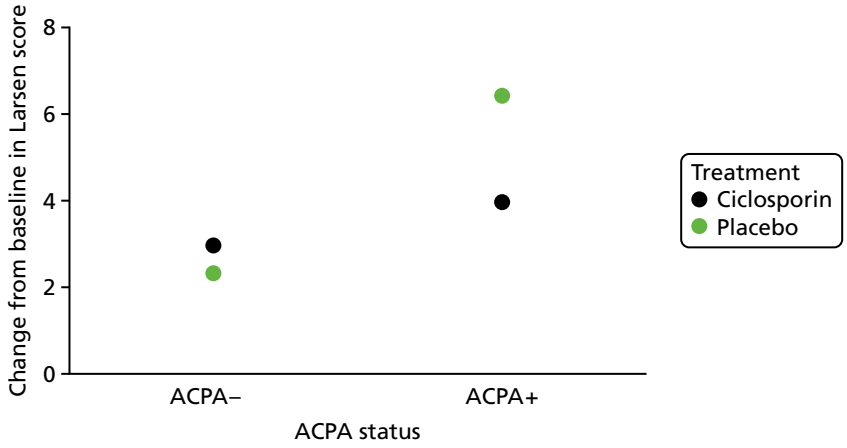

FIGURE 21 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 18 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

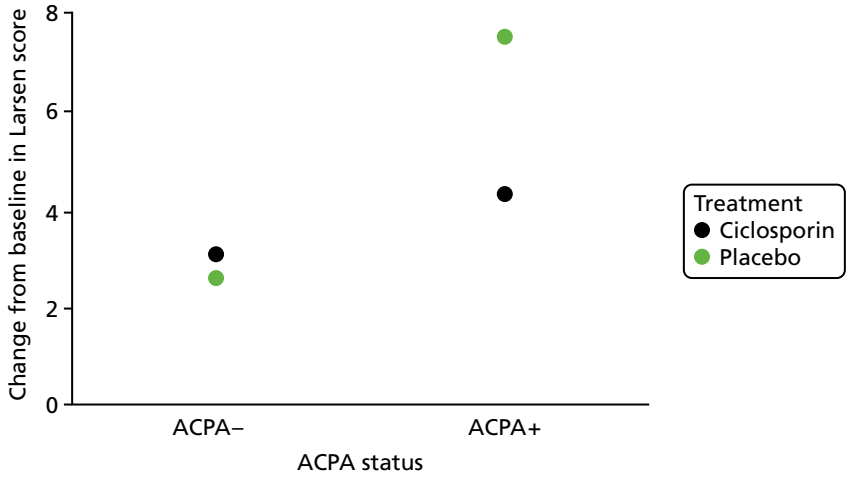

FIGURE 22 Anticitrullinated protein/peptide anti-body status–treatment interaction on erosions at 24 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

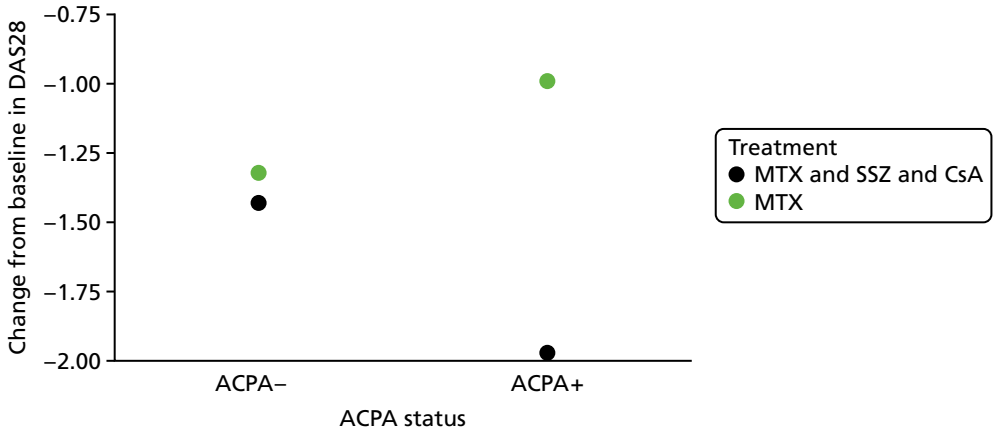

FIGURE 23 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 6 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

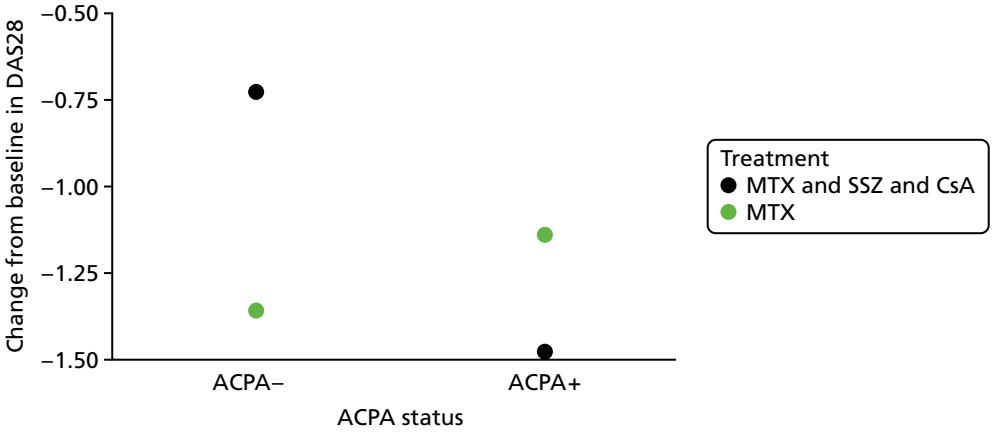

FIGURE 24 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 12 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

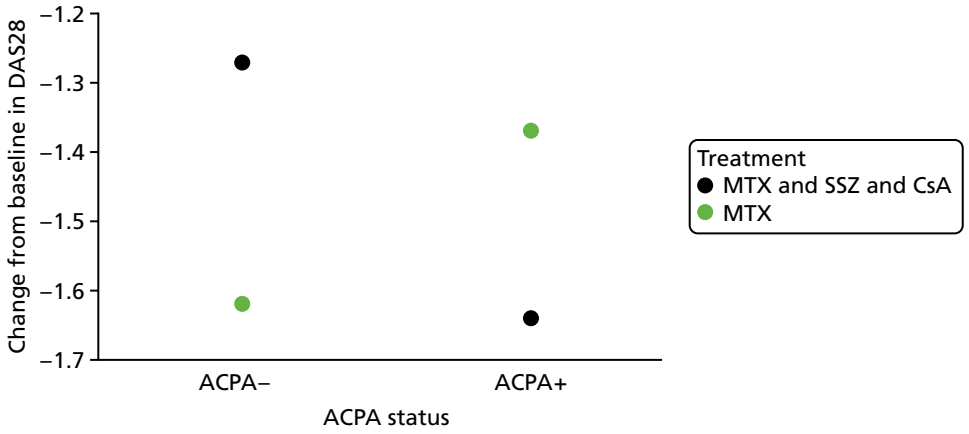

FIGURE 25 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 18 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

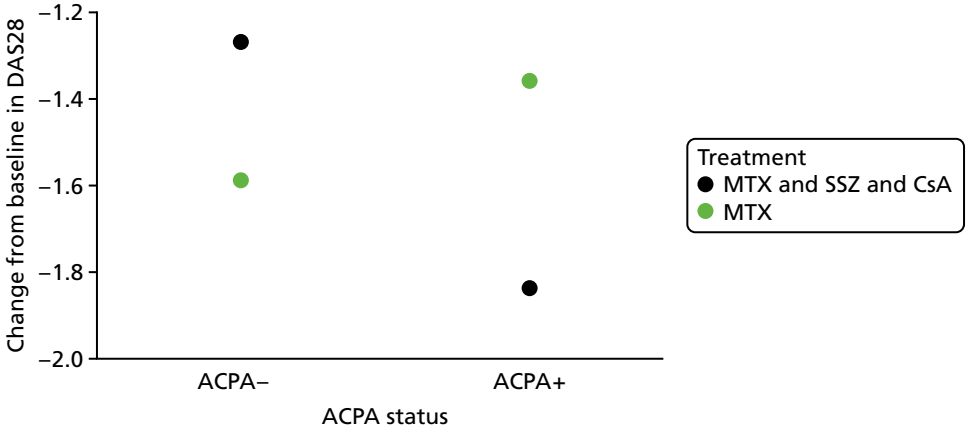

FIGURE 26 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 24 months from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

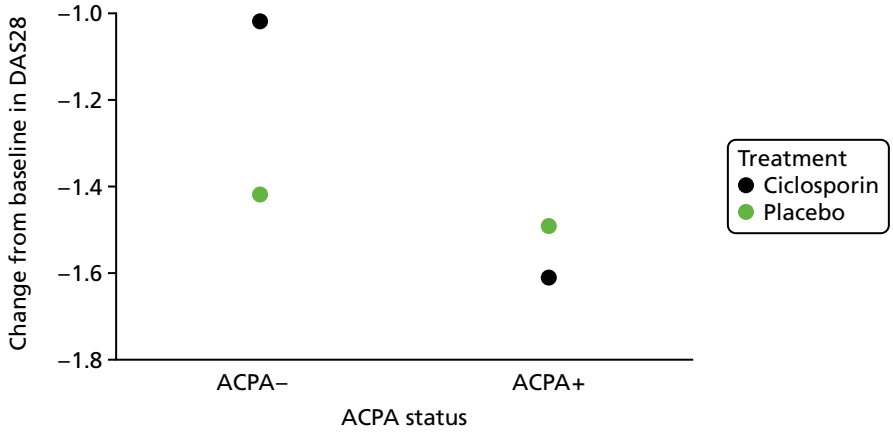

FIGURE 27 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 6 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

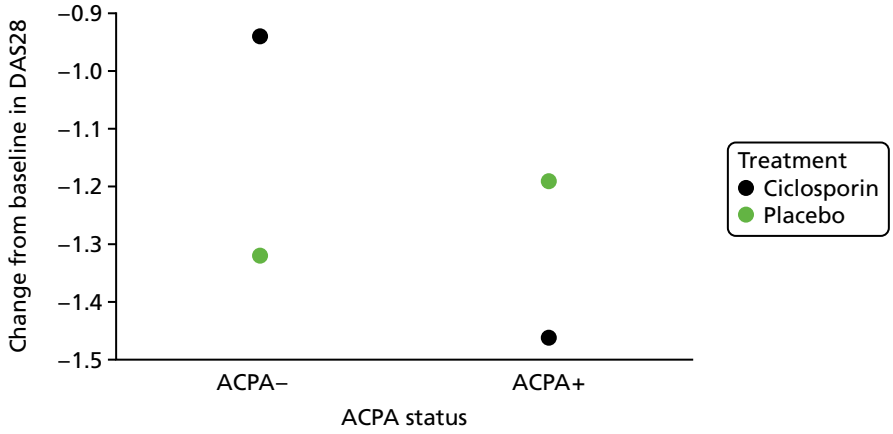

FIGURE 28 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 12 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

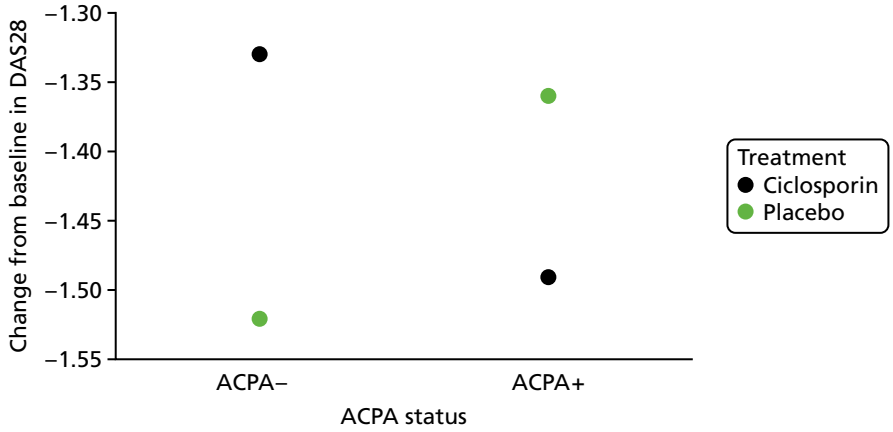

FIGURE 29 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 18 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

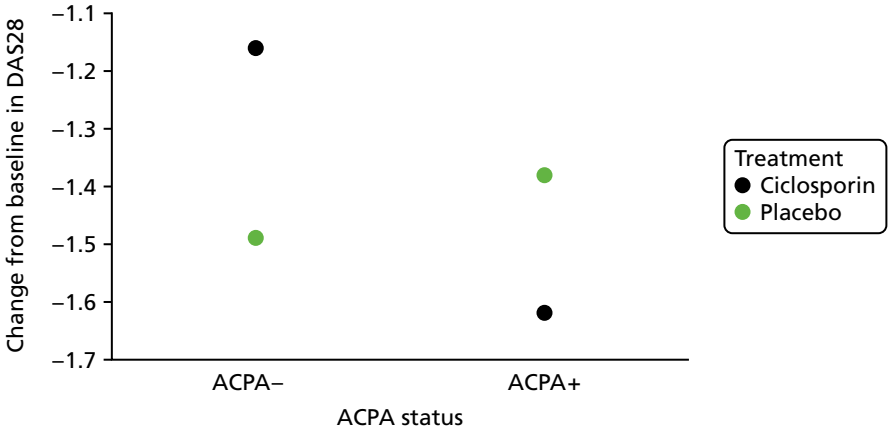

FIGURE 30 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 24 months (CsA vs. placebo) from Seegobin *et al.*[109] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive.

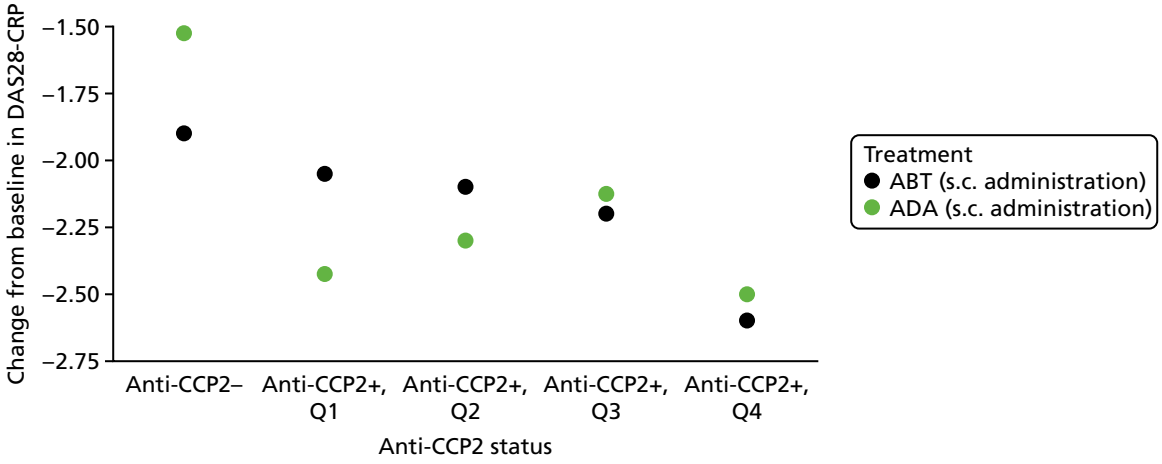

FIGURE 31 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 6 months from Sokolove *et al.*[110] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; Q, quartile; s.c., subcutaneous.

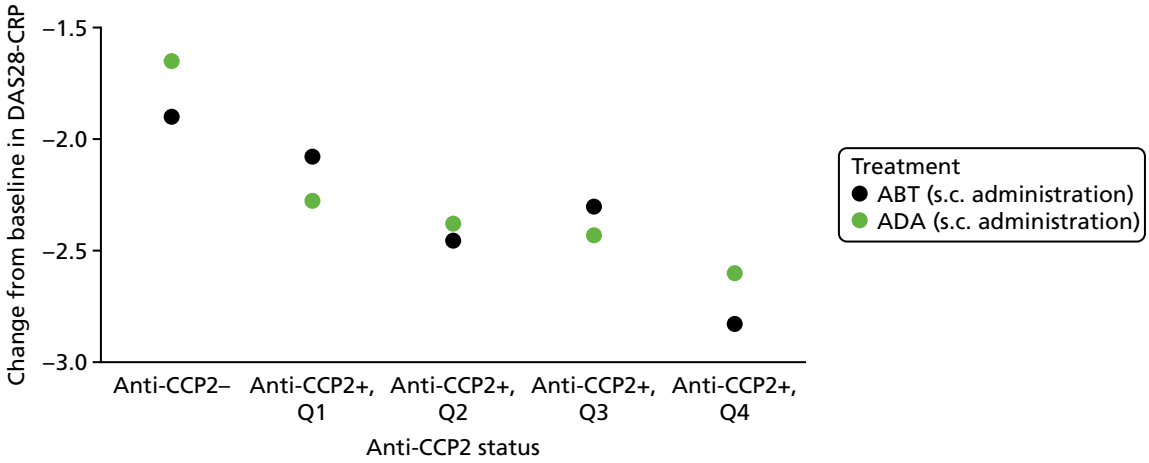

FIGURE 32 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 1 year from Sokolove *et al.*[110] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; Q, quartile; s.c., subcutaneous.

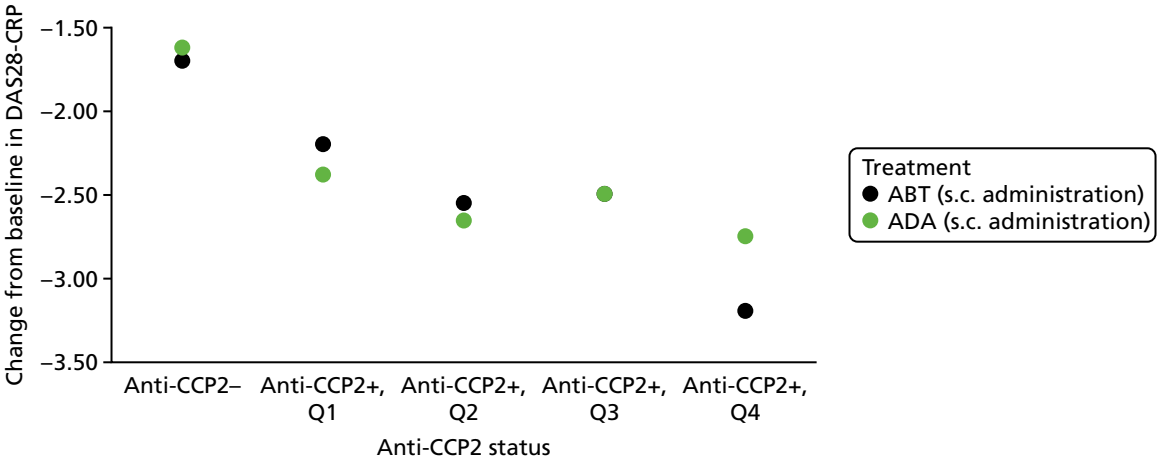

FIGURE 33 Anticitrullinated protein/peptide anti-body status–treatment interaction on disease activity at 2 years from Sokolove *et al.*[110] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; Q, quartile; s.c., subcutaneous.

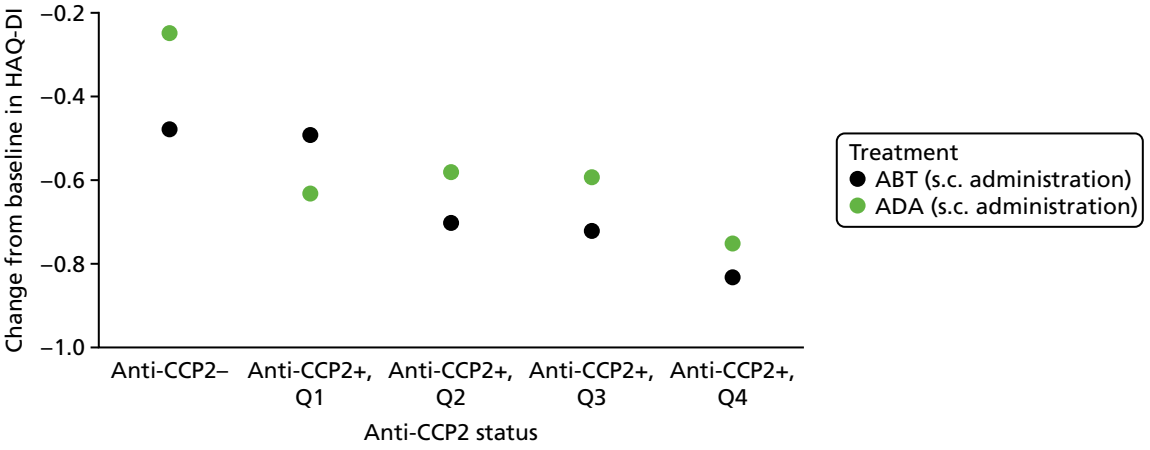

FIGURE 34 Anticitrullinated protein/peptide anti-body status–treatment interaction on physical function at 6 months from Sokolove *et al.*[110] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; Q, quartile; s.c., subcutaneous.

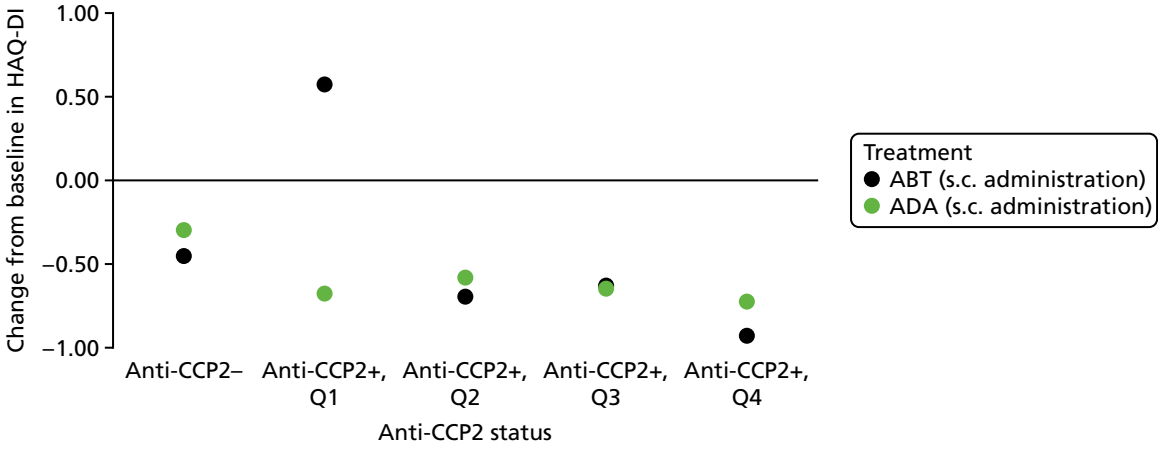

FIGURE 35 Anticitrullinated protein/peptide anti-body status–treatment interaction on physical function at 1 year from Sokolove *et al.*[110] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; Q, quartile; s.c., subcutaneous.

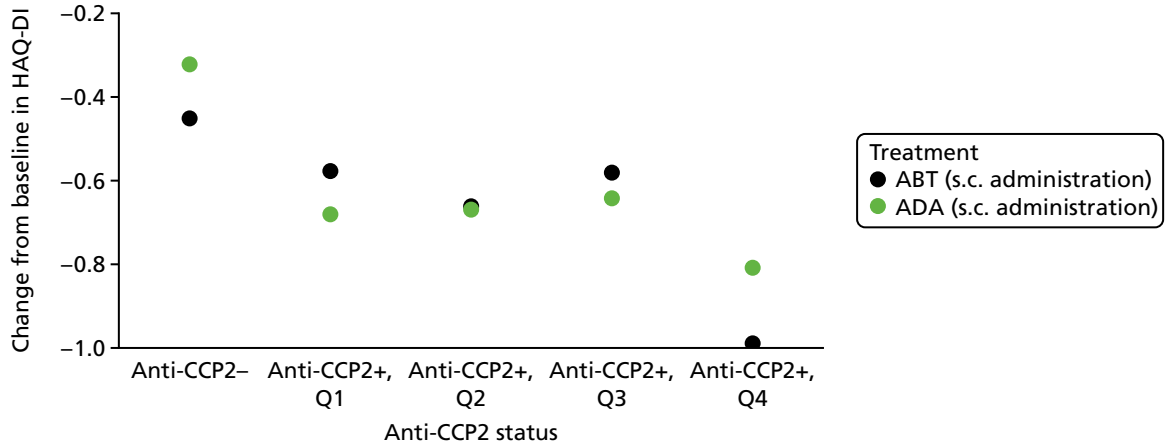

FIGURE 36 Anticitrullinated protein/peptide anti-body status–treatment interaction on physical function at 2 years from Sokolove *et al.*[110] ACPA–, anticitrullinated protein/peptide anti-body negative; ACPA+, anticitrullinated protein/peptide anti-body positive; Q, quartile; s.c., subcutaneous.

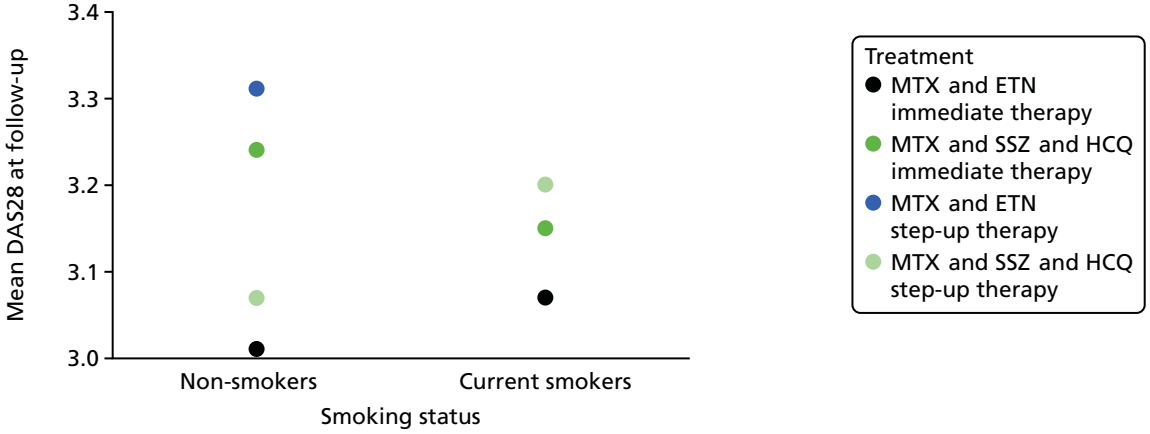

FIGURE 37 Smoking status–treatment interaction on disease activity at 1–2 years from Maska *et al.*[105]

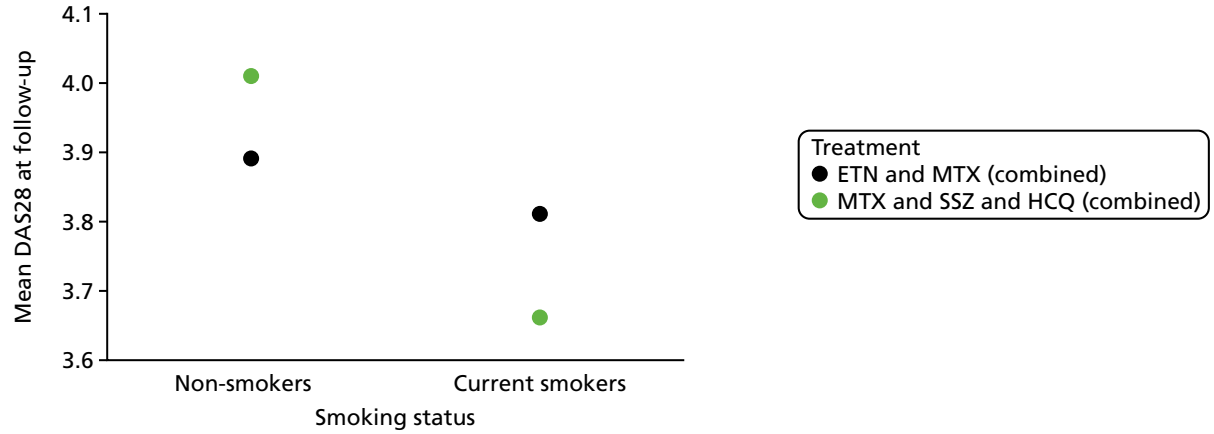

FIGURE 38 Smoking status–treatment interaction on disease activity at 24 weeks from Maska *et al.*[105]

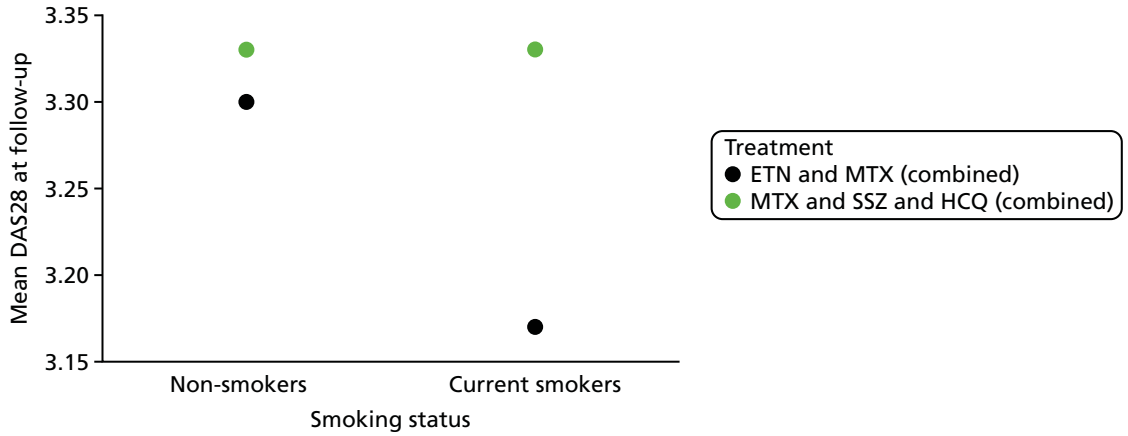

FIGURE 39 Smoking status–treatment interaction on disease activity at 48 weeks from Maska *et al.*[105]

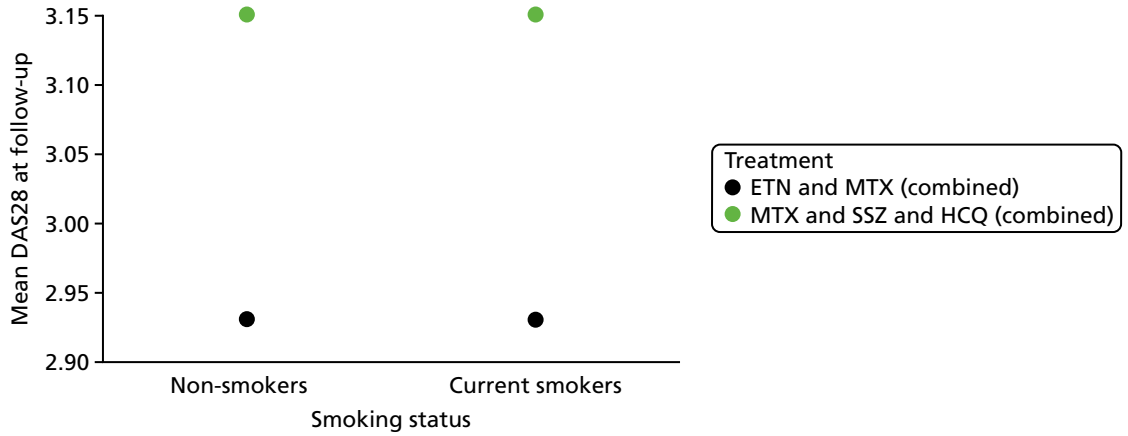

FIGURE 40 Smoking status–treatment interaction on disease activity at 102 weeks from Maska *et al.*[105]

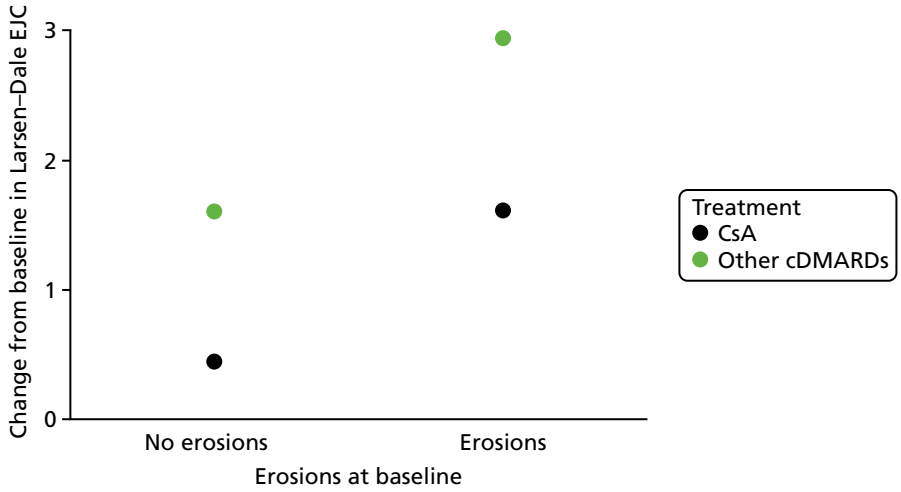

FIGURE 41 Erosion status–treatment interaction on radiographic progression (progression in the eroded joint count) at 12 months from Pasero *et al.*[107] EJC, eroded joint count.

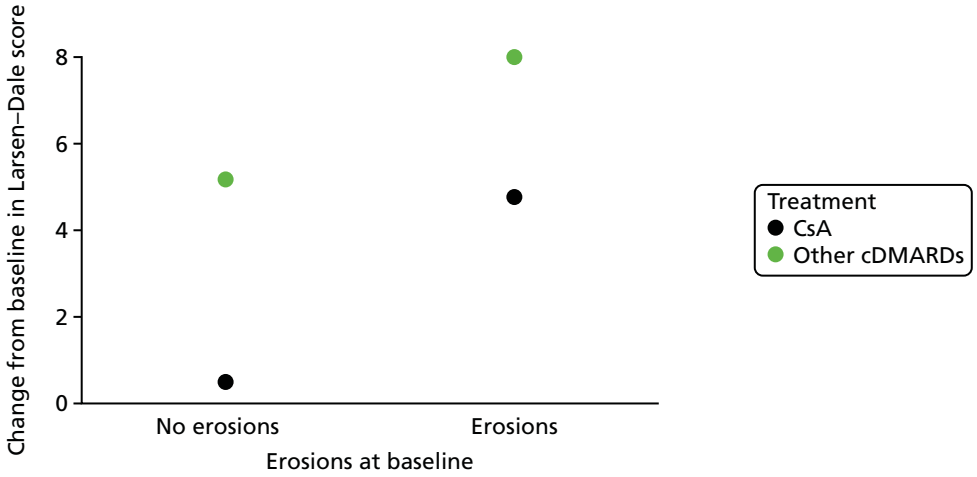

FIGURE 42 Erosion status–treatment interaction on radiographic progression (progression in the damage score) at 12 months from Pasero *et al.*[107]

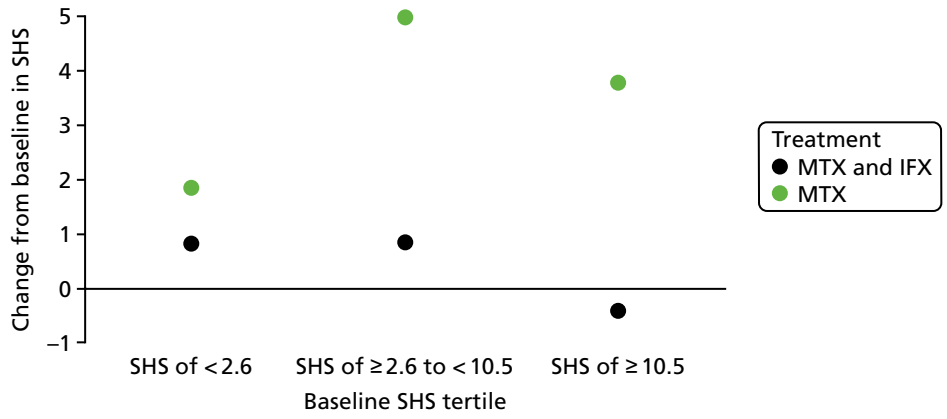

FIGURE 43 Radiographic score tertile–treatment interaction on radiographic progression at 54 weeks from Smolen *et al.*[100]

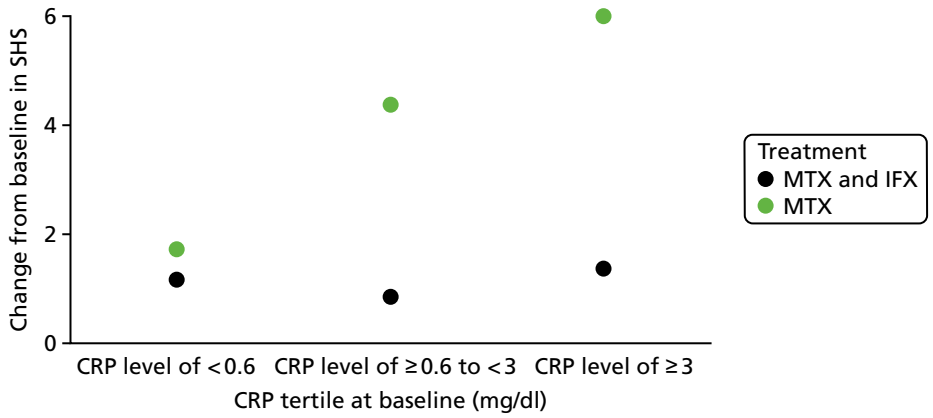

FIGURE 44 C-reactive protein tertile–treatment interaction on radiographic progression at 54 weeks from Smolen *et al.*[100]

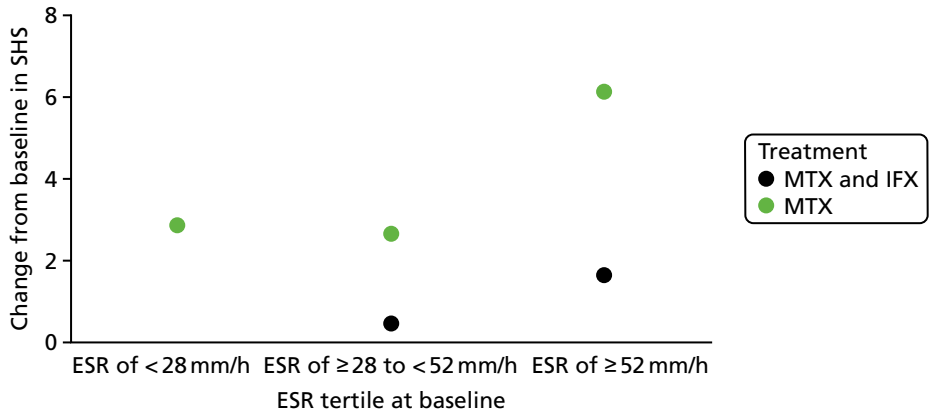

FIGURE 45 Erythrocyte sedimentation rate tertile–treatment interaction on radiographic progression at 54 weeks from Smolen *et al.*[100]

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