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Dear Meindert

RE: ADALIMUMAB, ETANERCEPT, INFLIXIMAB, CERTOLIZUMAB PEGOL, GOLIMUMAB, TOCILIZUMAB AND ABATACEPT FOR THE TREATMENT OF RHEUMATOID ARTHRITIS NOT PREVIOUSLY TREATED WITH DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS AND AFTER THE FAILURE OF CONVENTIONAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS ONLY: SYSTEMATIC REVIEW AND ECONOMIC EVALUATION (ASSESSMENT REPORT)

MSD welcomes the opportunity to comment on the Assessment Group (AG) report[1] which sets out the systematic review and economic modelling exercise undertaken by the AG.

MSD understands that the AG report is only one component of the evidence available to the Committee to aid its deliberations although, within the context of a multiple technology appraisal, it is usually seen as the more authoritative analysis. We are therefore concerned that the approach taken by the AG has departed so radically from that taken in all recent appraisals of these technologies. That this novel approach only considers 32% of the available clinical trial data, and disregards ACR data reported for over 12,000 patients would also appear to be at odds with the need to evaluate all available data as part of the HTA process.

We note that NICE is endeavouring to make the academic in confidence information related to the TACIT trial[2] (lead investigator, Professor David Lloyd Scott) available to stakeholders at the time of the Committee meeting and only then will we be able to understand the influence of this study on the overall assessment report.

Evidence to date demonstrates that there is a role for biological disease-modifying anti-rheumatic drugs (bDMARDs), based on clinically relevant greater improvement in physical function compared to treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs)[3].

Based on current NICE guidance, of the estimated 422,000[4] patients with rheumatoid arthritis (RA) in the UK, approximately 63,300[5] are currently eligible for bDMARD therapy. The understanding in MSD is that the current review was viewed as an opportunity to assess whether bDMARD therapy should be made available to more patients.

Anti-TNF therapies have been shown to be effective in patients with both severe and moderate disease; using an observational study of real-world patients Hyrich *et al.*[6] demonstrated, as early as 2009, that anti-TNFs provide clinically significant improvements in HAQ scores of a similar magnitude in both groups. Recommendation 1 of the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines on eligibility criteria for the first biological therapy[7] reflects this and states that *"biological therapies are recommended as options for the treatment of adults who have the following characteristics. (i) active RA as measured by DAS28 >3.2…"*. They go on to summarise the evidence base for this recommendation including evidence from observational cohorts which shows that sustained disease between a DAS28 score of 3.2 and 5.1 still translates into radiographical progression.

MSD agree with the BSR and BHPR recommendations and believe that when combined with the majority of available evidence demonstrating bDMARDs to be cost-effective treatment options for severe RA, the economic modelling exercises undertaken by the manufacturers and the AG showing similar cost-effectiveness results for the severe and moderate populations, and the long-term safety data for the anti-TNF drugs[8], the case for lowering the DAS28 threshold to 3.2 for access to bDMARDs in cDMARD-experienced patients is clear.

We have attached a detailed response to the AG report.

Kind regards,

[redacted]

[redacted]

MSD's concerns are focused around the following themes:

1. EULAR or ACR to inform the response criteria. The AG model relies on a EULAR response whereas the majority of the manufacturers' models and most previous NICE models have used ACR response.
    - Far fewer trials report EULAR response criteria (or data which can be used to calculate EULAR) so much of the evidence base is lost by excluding ACR studies.
    - Interchangeability of ESR or CRP to calculate DAS28 and then EULAR is assumed but evidence suggests that this is not appropriate.
2. Use of an analysis of the ERAS database for the HAQ progression on cDMARDs. All other NICE reviews have used a linear progression.
3. The results of the AG model are contradictory to the literature where bDMARDs are consistently shown to be cost-effective treatment options.
4. The systematic review and MTC have not been reported clearly and deviate from established practice, with an unclear impact on the analyses.
    - It is not clear how including academic in confidence TACIT data impacts the AG report's conclusions.
5. Unknowns within the AG report.
    - Due to confidentiality issues the AG have not shared their model and keep many data as academic in confidence; this hinders our ability to provide a full critique.

Further to this, we have also presented a brief response to the AG's critiques of the MSD modelling exercise and a list of factual inaccuracies identified in the AG report in Appendices 1 and 2 respectively.

Use of EULAR or ACR data to inform analyses

The AG model relies on a EULAR response whereas the majority of the manufacturers' models and most of the previous NICE models have used ACR response. We believe that this departure from precedent is inappropriate as far fewer trials report EULAR data and consequently, much of the evidence base is lost by excluding trials reporting ACR data. We recognise that UK clinicians are known to utilise DAS when assessing RA in clinical practice, in preference to ACR, however, it is important to note that robust evidence-based decision-making should utilise the entirety of the currently available evidence base.

The majority of trials identified from the AG systematic review and included within the MTC report ACR; only a minority of trials report EULAR. Of the 37 trials included in the MTC, 35 trials report ACR (95% of the total) and only 12 trials report EULAR (32% of the total). When the size of the trials contributing to the MTC (*i.e.* number of patients) is considered, 12,414 patients are from trials reporting ACR while only 3,923 patients are from trials reporting EULAR (plus an unknown number of patients from the TACIT trial). Note that these patient groups are not mutually exclusive, and that the 37 trials included in the MTC contained a total of 12,672 patients reporting ACR/EULAR (plus an unknown number of patients from the TACIT trial). Therefore, a large proportion of the current evidence base and reported patient experience is disregarded when ACR is not considered appropriately in the AG modelling.

We believe that as the EULAR analyses are informed by limited data and are therefore less robust than similar ACR analyses would be, the AG has deemed it necessary to bolster the EULAR analyses through the incorporation of additional trials that did not meet the inclusion criteria specified in the AG systematic review. For the EULAR analyses, four additional trials have been included and for the ACR analyses 14 additional trials have been included. However, despite the inclusion of these additional trials, the proportion of data that have been lost due to the AG's preference for EULAR remains unacceptably high; 49 trials report ACR (96% of the total) while only 16 trials report EULAR (31% of the total).

In conclusion, we find the AG's approach to the MTC to be completely antithetical to the guiding principle for such analyses, *i.e.* that conclusions should be informed by the greatest amount of appropriate data, pooled correctly (without unnecessarily and prejudicially discarding ACR data and without inappropriate consideration of trials that do not meet the AG's own criteria for inclusion).

In addition, we observe that as a consequence of using EULAR data, no conclusions could be reached from the MTC analysis for 'population 1' (only one trial reporting EULAR data was identified for this population). As the purpose of the AG report is to provide evidence-based analyses that can guide NICE decision-making, a reliance on EULAR data is counter-productive for the purposes of this assessment.

Although the AG has incorporated ACR data into the modelling through a sensitivity analysis, the approach involves the mapping of ACR to EULAR in a manner which is:

(i) Not clearly explained, *i.e.* has the mapping approach been applied to the summary results from the MTC analyses or to the ACR data reported by individual trials?

(ii) Not available for proper critique - as the mapping approach is informed by an academic in confidence database (VARA, a veterans' database from the US).

(iii) Not properly reflective of the clinical setting which is being considered - it is not clear how relevant VARA data are to the UK population and raises the further question of why these US data are appropriate when a US response score (ACR) has been deemed inappropriate by the AG.

Interchangeability of ESR or CRP to calculate DAS28 and then EULAR

On page 64 of the AG report, it is stated that *"It was assumed that DAS28-CRP and DAS28-ESR are interchangeable where only one is reported"*, with this assumption accredited to discussion with clinical advisors. However, there is evidence to support that DAS28-ESR and DAS28-CRP are not interchangeable[9,10]. The difference between the two measurements may have impacted which trials were classified as including patients with 'severe' RA. The AG report further states that *"If both were reported, DAS28-ESR was used as this was reported most regularly"*. Sensitivity analyses excluding the five trials exclusively reporting DAS28-CRP should be conducted in order to mitigate the risk that trials have been inappropriately pooled according to disease severity.

HAQ progression on cDMARDs

The AG use a modified version of the regression model in Norton *et al.* 2012[11] (which due to confidentiality issues we cannot fully evaluate), whereas all the manufacturer submissions and all previous NICE guidance rely on a linear progression of HAQ whilst on cDMARDs. The AG state that *"there appears to be little long term evidence to support the value used by the manufacturers"* however, they make this statement without conducting a systematic review of the literature.

MSD has undertaken a systematic review of the literature (described in Appendix 3) and has identified studies presenting data on HAQ progression. A number of these studies demonstrate a linear HAQ progression (either with or without an initial response to cDMARDs at 6 months)[12,13,14,15,16,17,18,19], while other studies demonstrate a "J-shaped" curve[20,21,22,23,24,25,26,11,27], *i.e.* a more rapid worsening of HAQ in the early stages of treatment with cDMARDs. In addition, others show that the nature of HAQ progression is variable[28,29,30], dependent on patient characteristics, suggesting that a single assumption for HAQ progression in modelling may not be appropriate. As a consequence of the disparate evidence base, MSD believes that there is considerable uncertainty surrounding the true HAQ progression on cDMARDs and believe that the sensitivity analysis applied by the AG of linear progression is at least as plausible as their basecase assumption.

The results of the AG model are contradictory to the literature

The following table summarises the conclusions drawn by the authors of the papers identified by the AG in their systematic review for cost-effectiveness studies. Only cost-utility analysis studies of bDMARDs with one or more cDMARDs as the main comparator have been presented, where the population is not cDMARD-naïve (to allow a comparison to the results of the AG's model).

Cost-effectiveness studies for bDMARD-naïve patients with RA (CUA studies compared to cDMARDs only)				
Study	**Drug**	**Comparator**	**Conclusion of authors**	**bDMARD(s) cost-effective?**
Bansback *et al*. 2005[31]	adalimumab	MTX	*"Adalimumab appears to be cost effective"*	Yes
Barbieri *et al*. 2005[32]	infliximab	MTX	*"This model suggests, with its underlying assumptions and data, that the combination of infliximab and MTX may be a cost-effective treatment"*	Yes
Barton *et al*. 2004[33]	infliximab/etanercept	cDMARDs	The ICER was dependant on a number of variables including the positioning of TNFα inhibitors in the clinical pathway and demographic and age of the starting population	No
Brennan *et al*. 2004[34]	etanercept	cDMARDs	*"the results suggest that etanercept is cost-effective when compared with non-biologic agents"*	Yes
Brennan *et al*. 2007[35]	TNFα inhibitors (infliximab/ adalimumab/ etanercept	cDMARDs	*"the analysis concludes that current practice for the use of TNF-α antagonist therapies, after RA patients have failed at least two traditional disease-modifying anti-rheumatic drugs, appear cost-effective"*	Yes
Chen *et al*. 2006[36]	TNFα inhibitors (infliximab/ adalimumab/ etanercept	cDMARDs	The ICER was dependant on the positioning of TNFα inhibitors in the clinical pathway and assumptions around HAQ data on early or late RA. The range was from £30-£64k	Uncertain
Jobanputra *et al*. 2002[37]	infliximab/etanercept	cDMARDs	Not cost-effective, but the article states *"it must be stressed that these figures do not include all benefits"*	No
Kobelt *et al*. 2003[38]	infliximab	cDMARDs	*"the cost-effectiveness ratios remain within the usual range for treatments to be recommended for use"*	Yes
Kobelt *et al*. 2004[39]	infliximab/etanercept	cDMARDs	*"For this patient group, cost effectiveness ratios are within the generally accepted threshold of €50 000"*	Yes
Kobelt *et al*. 2005[40]	etanercept	MTX	*"in this analysis, the cost per QALY gained with combination treatment with etanercept plus methotrexate compared with methotrexate alone falls within the acceptable range"*	Yes

Lekander *et al*. 2010[41]	infliximab	cDMARDs	*"Results from base-case and sensitivity analyses fell well below established benchmarks for cost-effectiveness in Sweden"*	Yes
Marra *et al*. 2007[42]	infliximab	MTX	*"Depending on the method for determining utility values used in the calculation of QALYs, very different incremental cost-effectiveness utility ratios are generated"*	Uncertain
Soini *et al*. 2012[43]	tocilizumab/ adalimumab/ etanercept	MTX	*"Tocilizumab + methotrexate is a cost-effective initial biologic treatment for patients with moderate-to-severe rheumatoid arthritis after failure with one or more tDMARDs"* It should also be noted that whilst tocilizumab was the most cost-effective, adalimumab and etanercept also had acceptable ICERs compared to MTX	Yes
Tanno *et al*. 2006[44]	etanercept	MTX	*"Using commonly applied thresholds for acceptable cost-effectiveness in the United States ($50 000 = ¥5.5 million/QALY) and the United Kingdom (£30 000 = ¥5.7 million/QALY), etanercept therapy in Japan can be considered cost-effective"*	Yes
Vera-Llonch *et al*. 2008[45]	abatacept	MTX	*"Abatacept is cost-effective by current standards of medical practice in patients with moderately to severely active RA and inadequate response to MTX"*	Yes
Welsing *et al*. 2004[46]	TNFα inhibitors	Leflunomide	The ICER was dependant on the positioning of TNFα inhibitors in the clinical pathway	No
Wong *et al*. 2002[47]	infliximab	MTX	*"Infliximab plus methotrexate for 54 weeks for rheumatoid arthritis should be cost-effective with its clinical benefit providing good value for the drug cost"*	Yes

From the table it can be seen that only three of the identified published papers present a conclusion that their analysis did not find bDMARDs to be cost-effective when compared to cDMARDs. The NICE Specification for Manufacturer/Sponsor Submission of Evidence June 2012[48] (section 7.10) requires that the results of the model are consistent with the literature and if not, that justification be provided. The results of the AG model are not consistent with the published literature and there is insufficient justification presented as to why they should be given more credence.

Issues with systematic review and MTC

There are a number of additional issues we noted concerning the conduct and reporting of the AG systematic review and MTC:

(i) On page 57 of AG report it is stated that "Details of keywords strategies are reported in Appendix 2", however, the strategies were not provided. This means that the systematic review methodology could not be subjected to proper review. For example, without knowing which Boolean operators were used to combine the disease and intervention terms in Stage 2, it is not possible to confirm whether Stage 2 was more stringent than Stage 1, *i.e.* requiring citations to be relevant both for disease and intervention.

(ii) The AG deviated from scope in the definition of population 1 (described on page 60). We are concerned that this decision was not shared with the manufacturers to inform their submissions which may lead to variability in inclusion/exclusion criteria.

(iii) On page 63 it is stated that "Trials with early escape were included only if an appropriate imputation of data as determined by the Assessment Group was employed for dealing with censorship". However, no further details are given on what is deemed appropriate or inappropriate. This seems arbitrary and it is not clear what impact this has on the analyses.

(iv) The employed statistical model to analyse ACR and EULAR is a multinomial model, recognising that the categories within these measures are mutually exclusive (described on pages 64-68). This model is advantageous in allowing for simultaneous analysis of all ACR/EULAR outcomes, which helps to strengthen inferences. However, the linkage which is imposed between outcome categories (e.g. between ACR20, ACR50, and ACR70) is strong. Although some flexibility is allowed by adding random-effects terms for this linkage across trials, some model bias may still occur. It would therefore be useful to compare the multinomial results with the binomial results.

Inclusion of academic in confidence TACIT data

Regarding the inclusion and exclusion of trials, we believe that it is inappropriate to include the TACIT trial within the AG report. The TACIT trial has not been published and, therefore, has not been subjected to peer-review which undermines the credibility of the data provided by this study. A sensitivity analysis performed with the TACIT trial excluded would demonstrate to what extent the TACIT data have influenced the conclusions of the report. We understand the need for confidentiality to protect future publication in journals but believe that the study report should be made available to interested stakeholders (who could act as an interim proxy for peer-review).

Unknowns within the AG report

Due to confidentiality issues the AG model has not been shared. Without the model it is not possible to provide a full critique of the approach the AG has taken to produce their report. A recent correspondence from NICE stated that this was due to confidential material marked in one of the manufacturer submissions. Based on the AG report we are unclear as to which confidential data have been used in the model that could not be stripped out and still provide a model shell for evaluation.

Within the report, key data are also kept academic in confidence and cannot be reviewed, *i.e.* Figure 95 on page 371 which relates to the HAQ progression on cDMARDS: a variable which the estimated ICERs are very sensitive to. Whilst a version of this figure is available in the Norton *et al*. 2012 paper[11], the actual relationship used in the AG model remains unavailable.

Table 187 on page 360 of the AG report is also marked academic in confidence. As explained above there is uncertainty around how the AG have undertaken their mapping exercise and the relationships which are redacted in this table could help interpretation of the methods used.

Appendix 1: Critiques of the MSD modelling

MSD deviances from the recommended method highlighted by the AG		
Page number	**Deviance from recommended method**	**Justification/clarification**
194	"MSD (golimumab and infliximab) and UCB (certolizumab pegol) assumed that tocilizumab would not be used following rituximab."	This was a deviation from the NICE treatment algorithm; however it would have impacted all evaluated technologies equally.
194/199	"MSD assumed in one strategy that rituximab could be used without a bDMARD have been provided previously."	This was an inclusion of rituximab in a position outside of its marketing authorisation. However, because only the cDMARD arm was affected, this erroneous positioning of rituximab was unfavourable to the bDMARDs as a group.
225	"The Assessment Group note that the tocilizumab costs are inaccurate, as a patient weighing between 46 and 50kg would be most inexpensively treated with a 400mg vial alone, an option not considered."	The cost calculations are not inaccurate for the weight groups specified and are based upon the upper weight limit of that group. Changing the weight group limits to incorporate these patients reduces the weighted average cost of tocilizumab by 0.68% and as such does not have a material effect on the ICERs produced by either model.
274	"MSD provides EQ-5D data for patients dependant on their health state… Substantially different values are provided for the golimumab submission and for the infliximab submission, with these data being assumed to apply to all interventions in the relevant submission."	The utility equation to produce EQ-5D utilities for each ACR health state depends on the HAQ scores from the trials for these health states. As different HAQ scores were observed in GO-FORWARD (golimumab) and ATTEST (infliximab) the utility scores for each ACR health state differed depending on which trial was informing the model. The HAQ scores are presented in table 45 and table 46 in the golimumab and infliximab submissions respectively.
329	"It is commented that for both submissions only Analysis 1 and Analysis 7 was undertaken. Analysis 7 does not meet the NICE scope as it combines RA patients with moderate to severe and severe disease."	On page 54 it states that "The NICE scope did not specify the definition of severe active RA and moderate to severe active RA". The following definitions were adopted by the AG "Severe active RA will be defined by a DAS28 score of ≥5.1 and moderate to severe active RA will be defined as a DAS28 score between 3.2 and 5.1". However, in previous NICE reviews of bDMARDs (TA130, TA225, TA186, TA247, TA280) these technologies have been reviewed within their licences of moderate to severe RA which was a population including both moderate and severe patients

		(those with a DAS28 ≥3.2). Therefore, we would argue that the populations specified in the scope were; moderate to severe active RA with a DAS28 of ≥3.2 and severe active RA with a DAS28 of ≥5.1 and the AG has defined the thresholds for moderate and severe active RA respectively. We note that the majority of manufacturers have the same interpretation as the AG and feel that both definitions can be used to inform a decision on whether the DAS threshold should be lowered to allow access to patients with moderate disease (DAS28 ≥3.2).
329	"The Assessment Group note that MSD makes no comment on the discrepant absolute QALY values in the submission".	As explained above, the utility equation is dependent on the trial data driving the model. The resulting differing utilities drive the differences in total QALYs observed (in the region of 8 for the golimumab submission and in the region of 6 for the infliximab report).

Appendix 2: Factual inaccuracies

Factual inaccuracies		
Page number	**Inaccuracy**	**Comment**
52	Golimumab dosing: *"50 mg below 100 kg, 100 mg above 100 kg per month"*	Not all patients over 100 kg are eligible for the 100 mg dose. The wording from the SPC is as follows: *"In patients weighing more than 100 kg who do not achieve adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered…"*
52	Costing of adalimumab, etanercept, golimumab, infliximab and certolizumab in Table 3 of the AG report	MSD believes there is a lack of clarity around the cost calculations and the actual annual acquisition cost (including administration cost) should be as follows: Adalimumab: (26*352.14)+(26*3.05) =£9,234.94 Certolizumab yr1: (20*357.50)+(20*3.05) =£7,211.00* Certolizumab yr2+: (26*357.50)+(26*3.05) =£9,374.30 Golimumab: (12*762.97)+(12*3.05) =£9,192.24 Etanercept: (52*178.75)+(52*3.05) =£9,453.60 Infliximab: Unclear how averages have been calculated from BSRBR weight groups Abatacept/Tocilizumab: Cannot be checked due to CIC It is counterintuitive for golimumab to have a higher acquisition cost than adalimumab given the list prices and number of doses required per year. *includes PAS giving first 10 doses free. All these calculations rely on the fact that the administration costs in table 3 in the AG report are correct (see below).

52/355	On page 52 the administration cost per subcutaneous treatment is listed as £3.05 whereas on page 355 it is stated as £2.61.	It is unclear which of the two costs is correct.
219	"none of MSD, Pfizer and UCB include patient access schemes for tocilizumab or abatacept as these are commercial-in-confidence."	The tocilizumab PAS was provided in confidence to other manufacturers by Roche and was incorporated into the cost calculations in our submission. Only BMS refused to share details of their scheme and as such the abatacept PAS could not be incorporated.
354	"the cost of the interventions are detailed in Table 185."	Table 185 only contains the costs for cDMARDs and rituximab.
multiple	Throughout the document figures and tables are incorrectly referenced in the text or have incorrect titles. *i.e.* Figures 68 and 69 have the same title/on page 365 it states that "*figure 93 shows the average HAQ in the sample by EULAR response"*. This is actually presented in Figure 94 with Figure 93 providing mean EULAR mapped from ACR trials.	Incorrect labeling and cross-referencing has made the AG report harder to read and review.

Appendix 3: Systematic review of HAQ progression

A systematic literature review was performed to identify the relevant evidence base relating to HAQ progression for patients receiving treatment for RA with cDMARDs.

The following databases were searched using the ProQuest platform, with no date restrictions applied: MEDLINE®, MEDLINE® In-Process, Embase®, Embase® Alert. The following search strategy (Table 1) was used to identify citations from the specified databases:

Table 1: MEDLINE®, MEDLINE® In-Process, Embase®, Embase® Alert search strategy (Search conducted 13/09/2013)

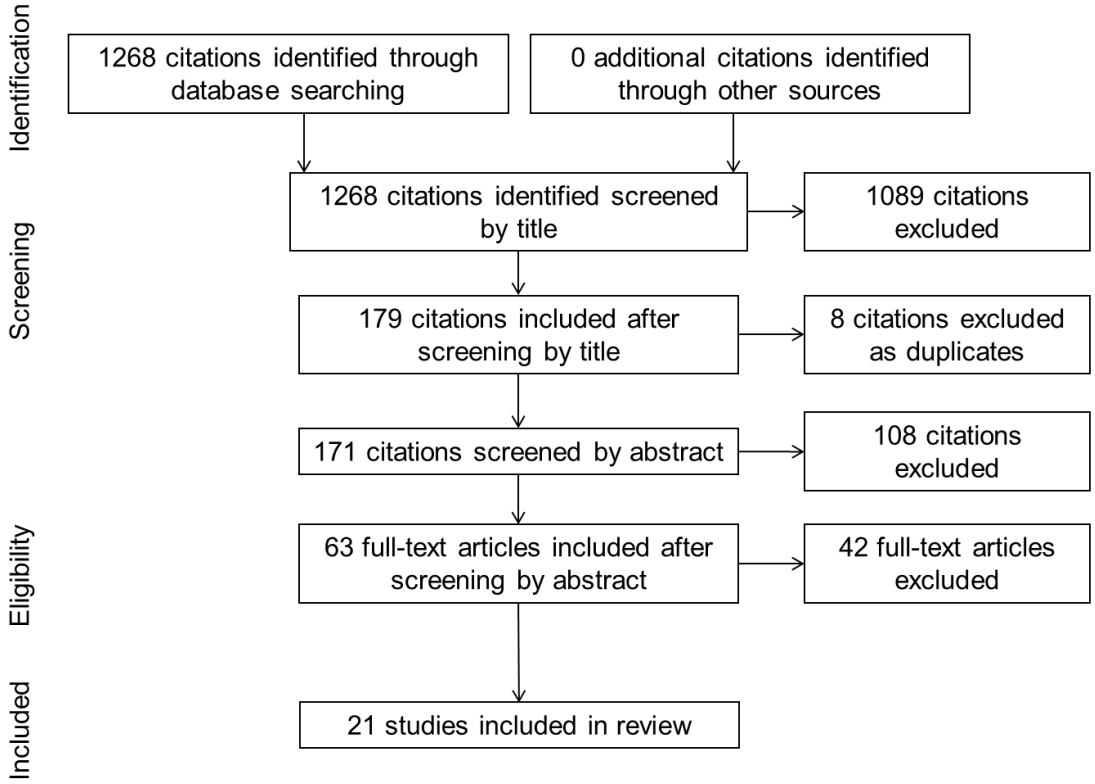
1	EMB(“rheumatoid arthritis”) OR MESH(“arthritis, rheumatoid") OR ti,ab("rheumatoid arthritis" OR "rheumatic arthritis" OR rheumarthritis)
2	ti,ab((chang* OR increas* OR decreas* OR deteriorat* OR improv* OR progress*) NEAR/5 (“Health Assessment Questionnaire” OR HAQ OR “HAQ score”))
3	ti,ab((functional NEAR/1 (ability OR disability OR status OR outcome[*1])) AND (“Health Assessment Questionnaire” OR HAQ))
4	2 OR 3
5	1 AND 4
6	5 AND la.exact("English")

To meet inclusion criteria, citations had to include adult patients with RA, who were treated with cDMARDs (no treatment with bDMARDs). The citations had to report HAQ scores (derived from ≥2 years of follow-up with a minimum of three follow-up points).

Two independent reviewers assessed the citation titles for eligibility, with discrepancies in decision-making resolved through consensus discussion between the reviewers. For citations included after title screening there then followed a further round of review of the abstracts (again conducted by two independent reviewers, with consensus discussion). For those citations deemed eligible after abstract screening, full-text versions were ordered to enable more detailed assessment, again by two independent reviewers with discrepancies resolved through consensus discussion and critical review of the list of included studies by a third independent reviewer.

A flow diagram describing the search results and study selection process is shown in Figure 1.

Figure 1: Flow of citations through screening process



Of the 1268 studies identified through the systematic literature review 21 studies were relevant to the decision problem. The included studies are listed below in Table 2:

Table 2: Included studies

Author	Year	Title
Norton *et al.*[11]	2013	Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality
Drossers-Bakker *et al.*[12]	1999	Long-term course and outcome of functional capacity in rheumatoid arthritis. The effect of disease activity and radiologic damage over time
Glennas *et al* [13]	2000	Recent onset arthritis in the elderly: A 5 year longitudinal observational study
Krishan *et al.*[14]	2004	Percentile benchmarks in patients with rheumatoid arthritis: Health assessment questionnaire as a quality indicator (QI)
Wolfe & Cathey[15]	1991	The assessment and prediction of functional disability in rheumatoid arthritis
Camacho *et al.*[16]	2011	Influence of age and sex on functional outcome over time in a cohort of patients with recent-onset inflammatory polyarthritis: Results from the Norfolk Arthritis register
Symmons *et al.*[17]	2006	Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs- results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial
Hawley & Wolfe[18]	1992	Sensitivity to change of Health Assessment Questionnaire (HAQ) and other clinical and health status measures in rheumatoid arthritis
Symmons *et al.*[19]	2005	The British Rheumatoid Outcome Study Group (BROSG) randomised

		controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis
Svensson *et al.*[20]	2013	Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria
Wolfe[21]	2000	A reappraisal of HAQ disability in rheumatoid arthritis
Descalzo *et al.*[22]	2012	Effectiveness of a clinical practice intervention in early rheumatoid arthritis
Munro *et al.*[23]	1998	Improved functional outcome in patients with early rheumatoid arthritis treated with intramuscular gold: results of a five year prospective study
Plant *et al.*[24]	2005	What factors influence functional ability in patients with rheumatoid arthritis. Do they alter over time?
Kalden *et al.*[25]	2003	The efficacy and safety of leflunomide in patients with active rheumatoid arthritis
Van den Broek *et al.*[26]	2012	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
Porter *et al.*[27]	1994	Outcome of second line therapy in rheumatoid arthritis
Bjork *et al.*[28]	2007	Hand function and activity limitation according to health assessment questionnaire in patients with rheumatoid arthritis and healthy referents: 5-year followup of predictors of activity limitation (The Swedish TIRA Project)
Odegard *et al.*[29]	2006	Association of early radiographic damage with impaired physical function in rheumatoid arthritis
Young *et al.*[30]	2000	How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS)
Van Vollenhoven *et al.*[49]	2010	Impact of rheumatoid arthritis disease duration and severity on ability to regain normal physical function with treatment

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