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Health economic modelling of treatment sequences for rheumatoid arthritis: a systematic review

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Abstract

The objective was to assess and critique how sequential disease modifying therapies (DMARDs) have been modelled in the context of economic evaluations of the use of DMARDs for the treatment of Rheumatoid Arthritis (RA). A secondary aim was to identify the methodological challenges of modelling sequential therapies.

Systematic searches of 10 databases were undertaken in February 2013. Studies were included if they were English language and reported a full comparative economic evaluation, and they were appraised using the Drummond checklist. Data extracted included economic evaluation data, data relating to sequential treatments, and data on the modelling methods used.

57 studies were identified, with 25 (44%) modelling a sequence of treatments. 43 (75%) were cost-utility analyses. 11 (19%) were UK, and 11 (19%) were US. The remainder were mainly European (26 (46%) studies). There was a distinction between studies in recent-onset RA (14 (25%)), and those in established RA (42 (74%)). One study (1%) was unclear. Individual level models were more likely to meet the Drummond criteria and evaluate sequences. No study identified an optimal sequence of multiple treatments given a set of alternative treatments. The level of reporting about the methods and evidence used to assess the impact of future treatments was generally poor. Where models considered a lifelong time horizon and downstream treatment sequences, evidence gaps were identified.

The review identified that methods have not been consistently applied, leading to varied estimates of cost-effectiveness. Treatment sequences have not been fully considered and modelled, potentially producing inaccurate estimates of cost-effectiveness.

Health economic modelling of sequential therapies for rheumatoid arthritis

1. Introduction

Rheumatoid Arthritis (RA) is a chronic, progressive, autoimmune disease affecting approximately 0.8% of the adult population.[1] RA affects the physical, psychological and social health of patients and is associated with premature mortality.[2] The typical age of onset is 40 years, and therefore there is a substantial effect on direct health costs, and societal costs associated with productivity lost.[3] Current management of RA involves disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids to retard disease progression. Analgesics and anti-inflammatories are used to treatment symptoms.

Conventional DMARDs (cDMARDs), including methotrexate, sulfasalazine and leflunomide, are relatively inexpensive and represent a small proportion of the overall cost of treating RA.[4] Newer 'biologic' DMARDs (bDMARDs) have had a substantial impact on patient care. The effectiveness of tumor necrosis factor-α (TNF-α) inhibitors – infliximab, adalimumab and etanercept – has been established in randomised controlled trials (RCTs)[5–12] and confirmed in meta analyses.[13–15] More recently, bDMARDs with alternative mechanisms such as rituximab, tocilizumab, and abatacept, along with new TNF- α inhibitors -certolizumab pegol and golimumab - have come to market. The optimal use of bDMARDs in the care pathway is subject to debate, in part because of their high cost. The UK National Health Service (NHS) currently allow bDMARDs only after ≥2 cDMARDs have been trialled and failed.[16]

Although RCTs represent the gold standard for estimating a treatment's relative effectiveness, short-term RCTs are not sufficient for estimating long-term cost-effectiveness in a chronic disease like RA. It is therefore necessary to synthesise evidence from several sources, including expert estimates, into a mathematical model to estimate costs and benefits over a lifetime. These mathematical models (known as decision-analytic models) are a simplified representation of reality, and describe the long term experience of a patient, and capture the costs and patient health related quality of life over time. Modelling now plays a crucial role in undertaking economic evaluations and informing health resource allocation decision making.[17]

In RA, differing methodologies have been used to evaluate cost-effectiveness of DMARDs.[18] This has resulted in inconsistent evaluations of the same treatments in similar populations, and debate regarding the most appropriate methods and evidence to be used to inform decision analytic models. A particular problem has been the sequencing of DMARDs, where failure on one DMARD leads to a switch to another DMARD. This has caused a move away from pair-wise comparison of small numbers of treatments, to the comparison of lifelong sequences of treatments.

The objective of this systematic review is to summarise the existing economic evidence for the use of DMARDs in RA. The review will assess the strengths and limitations of specific economic evaluations, and will draw generalised conclusions regarding the methodologies currently used to evaluate treatment sequences for RA.

2. Review Methodology

Systematic searches of online databases were undertaken to identify all economic evaluations of DMARDs for RA published in English. To ensure a high sensitivity, the search was developed by applying economic terms to

a general disease search for RA and DMARDs. The disease component of the search was based on a strategy for the NICE Rheumatoid Arthritis guideline.[19] Database filters to identify economic evaluations were used from the InterTASC Information Specialists' Sub-Group (ISSG) website (www.york.ac.uk/inst/crd/intertasc/). The search strategy was reviewed by an information specialist.

Studies published any time up to February 2013 were identified by searching BIOSIS, Cochrane (Database of Systematic Reviews, Databases of Methodological Reviews, Central Register of Controlled Trials), DARE, CINAHL, Embase, MEDLINE, NHSEED and SCI-WoS. Econlit was not searched due to good coverage of the other databases. Studies were included if they met the following criteria; (i) were economic evaluations of interventions targeting a change to the disease of people with RA; (ii) included a comparison of costs and benefits based on outcomes data or undertaken using decision-analytic methods; (iii) reported costs and health outcomes. Partial or non-comparative economic evaluations were excluded, as were conference abstracts, methodological papers, studies without cost and effectiveness outcomes, and non-English language papers. Studies were appraised using the Drummond 'Critical appraisal of a published article' checklist.[20] This checklist was chosen due to being a commonly used and validated economic evaluation appraisal tool. Data extracted included general economic evaluation data (analytical approach, population, interventions of sequences, time horizon, treatment history, health economic results). Data were also extracted concerning the treatment sequences modelled, and how this was undertaken. Data on any modelling methods used were also extracted. Systematic reviews of economic evaluations in RA were cross-checked to ensure all relevant articles were found.

3. Search Results

A total of 57 evaluations were included in the review. A PRISMA diagram detailing the selection of studies is provided in Figure 1. 43 (75%) were cost utility analyses (CUA's) with quality adjusted life years (QALYs) as the metric of health outcome. 11 (19%) studies used a UK perspective, and 11 (19%) a US perspective. The remaining studies are mainly from Europe (26 (46%)). 14 (25%) studies were in patients with recent-onset RA (no previous DMARD therapy). 42 (74%) of studies are in patients with established RA (prior DMARD therapy). One study (1%) was unclear with regard to whether the treatment was for recent-onset or established RA. Table 1 provides a summary of the recent onset studies (and the unclear study), and Table 2 provides a summary of the established RA studies.

4. Critical appraisal of studies in recent-onset RA

This section presents a critical appraisal of the 14 studies providing economic evidence for treatments of recent-onset RA.[21–34]

4.1 Scope of the economic evaluations of disease-modifying therapies in recent-onset RA

The summary details for all of the recent-onset RA economic evaluations are presented in Table 1. All 14 studies were CUA's, with effects quantified as QALYs. 10 (71%) of the studies considered the initiation of a particular therapy,[21,22,24,25,27–31,33] and four (29%) studies considered the tapering or adjustment of a treatment or combination of treatments.[23,26,32,34]

The studies were diverse in their treatment considerations, and since 2006 seven studies (50%) have evaluated the use of bDMARDs in recent-onset RA.[21–23,25,27,28,34] Prior to 2006, six studies(43%) were published which evaluated the economic impact of cDMARDs[24,26,29–31,33]. This leaves one study (7%) evaluating cDMARDs within a decision space where bDMARDs are used, and with a lifelong time horizon.[32] 2006 was approximately when the evidence for bDMARDs had matured after launch in the early 2000s, and so there was understandably a shift in the focus of economic evaluations from cDMARDs to bDMARDs to determine their cost-effectiveness. The NICE guidance for adalimumab, etanercept and infliximab was published in 2007.[16]

Six (43%) of studies were explicitly reported as being in an active RA population.[21,24,29,32–34] The disease severity in the patient population being evaluated was not clearly reported across all of the studies. Kobelt et al. (2011) evaluated etanercept plus methotrexate against methotrexate in a severe RA population,[25] and Kobelt et al. (2002) was an evaluation of methotrexate plus sulfasalazine against leflunomide in any patient with RA.[30] In the remaining six (43%) studies, the patient population and disease severity was not reported.[22,23,26–28,31]

Only five (36%) of the recent-onset RA studies had a lifelong time horizon for the economic evaluation.[21–23,28,32] Of these five studies, four were evaluations of bDMARDs in recent-onset RA, and all four used decision-analytic modelling methods to estimate costs and effects.[21–23,28] This included Chen et al. (2006), a publication of the independent submission made by a NICE Technology Appraisal Group based at Birmingham.[21] Only one study considered the lifetime costs and effects of alternative cDMARD monotherapy and combination therapy strategies in recent-onset RA.[32] Four studies (29%) had a time horizon of no more than two years.[24,29,31,34] A truncated time horizon of this magnitude is likely to omit future costs and effects that occur between alternative treatments, and in particular if a DMARD therapy is assumed to have a disease-modifying effect on the future course of a chronic condition in RA. Therefore, the short time horizon is likely to lead to inaccurate estimates of lifetime cost-effectiveness.

10 of the 14 (71%) studies used decision analytic modelling methods to determine expected costs and QALYs.[21–23,25,26,28,30,32,33] The remaining four studies (29%) were economic evaluations alongside clinical trials.[24,29,31,34] Prior to 2006, six studies (43%) evaluated the economic impact of cDMARDs, with none having a time horizon of longer than 10 years.[24,26,29–31,33] Three of the six studies (50%) undertook an economic evaluation alongside a clinical trial.[24,29,31] Which partially explains the short time horizon. The extrapolation or modelling of costs and effects may not be the primary objective when reporting a clinical trial; however the results of these studies will be of restricted use for resource allocation decision-making.

4.2 Downstream costs and effects in recent-onset RA

In the five studies with a lifelong time horizon for the economic evaluation, only Chen et al. (2006) explicitly modelled a downstream sequence of treatments.[21] The analysis allowed a consideration of multiple positions

of bDMARDs. However the authors did not attempt to identify an optimal treatment sequence from the available treatment set.

Of the remaining four studies, Tosh et al. (2011) considered alternative cDMARD monotherapy and combination therapy strategies in recent-onset RA.[32] TNFα's were not considered at this divergence point, due to the evaluation being used to inform the NICE Clinical Guideline, and the NICE guidance at that time recommending that TNFα's only be used after treatment failure with at least two cDMARDs.[19] The lifelong time horizon would have allowed the implications of faster access to bDMARDs (by using combination rather than sequential monotherapy cDMARDs) to be quantified, however the downstream bDMARDs were not explicitly modelled, and instead estimates of expected costs and QALYs were added on. Spalding et al. (2006) used a pooled estimate of costs and effects to provide evidence of the downstream sequence after comparing the first line use of bDMARDs.[28] Finckh et al. (2009) compared symptomatic care with methotrexate and bDMARDs, and did not clearly report how future costs and QALYs after treatment failure were estimated.[23] Davies et al. (2009) evaluated bDMARDs at first line position in an explicit sequence; however they did not clearly report how evidence was used to determine the cost and QALY impact of these future treatments.[22]

From the nine studies with a truncated time horizon, five explicitly included a downstream sequence of treatments.[25–27,33,34] Kobelt et al. (2011) evaluated etanercept plus methotrexate compared to methotrexate monotherapy over a 10 year time horizon, with a downstream sequence of two bDMARDs and then progression to a standard therapy extrapolation of costs and disease activity.[25] Both Maetzel et al. (2002)[26] and Schadlich et al.(2005)[33] evaluated the impact of adding leflunomide to a cDMARD sequence at second line, over a five year and three year time horizon, respectively. Neither study evaluated the cost-effectiveness of adding leflunomide at alternative positions in the sequence. Schipper et al. (2011) evaluated the cost-effectiveness of allowing sequential bDMARD use in recent-onset RA, over a five year time horizon.[27] After bDMARD use the model contained a transition to combination cDMARDs, however the impact of this on costs and effects was not reported. Van den Hout et al. (2009) compared monotherapy and combination cDMARD therapies with initial infliximab plus methotrexate therapy, over a two year time horizon.[34] The analysis was an economic evaluation alongside a clinical trial, and in the trial patients progressed to another active therapy after a failure. The trial was reported as Intention to Treat (ITT), and so the costs and effects of transition to downstream sequential therapies were included in the economic evaluation.

Four studies remain with a truncated time horizon and no explicit inclusion of downstream costs and effects.[24,29–31] All four studies are relatively old (1998-2004) and are evaluations of cDMARDs. For these treatments, there was less of a focus on future benefits such as disease control and joint damage, and more of a focus on a short term reduction in disease activity. Three of the four studies were clinical trials,[24,29,31] and only Kobelt et al.(2002) used a decision analytic model to estimates costs and effects over a 10 year time horizon.[30]

4.3 Decision-analytic modelling methods in recent-onset RA

10 of the 14 (71%) studies used decision analytic modelling methods to determine expected costs and QALYs.[21–23,25,26,28,30,32,33] Two of the 10 models (20%) used decision trees,[26,33] four studies (40%)

were cohort Markov/State-transition models,[25,27,28,30] and four studies (40%) are individual patient models.[21–23,35]

The decision tree model by Maetzel et al. (2002) had a five year time horizon and was capable of modelling a sequence of six explicit treatments.[26] However this modelling method required simplifications which lead to limitations of the final analysis. In particular, only one level of response was incorporated (ACR20), with the authors recognising that incorporating ACR50 would have allowed the potential superiority of newer DMARDs to be quantified in the model. Also, the model only incorporated approximate direct costs over the long term. The decision tree model by Schadlich et al. (2005),[33] had a three year time horizon and was very similar to that of Maetzel et al. (2002).[26] It suffered from the same limitations, and also from the fact that it did not account for disease duration or diminished clinical response for cDMARDs used at later points in the sequence.

The four Markov models defined health states and transition probabilities to move through different states. Two defined these health states by health assessment questionnaire (HAQ) score, one by disease activity score (DAS) score, and one simply by either being on an active treatment or dead,[26] and with time dependent costs and utilities.[31]

The four individual sampling models explicitly modelled sequential treatments and all fully met the Drummond criteria.[21–23,32] Tosh et al (2011)[32] and Davies et al. (2009)[22] used a regular six-month time cycle to update costs and QALYs. This represented a simplification of evidence, in particular when events can occur at any time, or when regular events (such as treatment re-administration) occur outside of the six-month cycle. Chen et al. (2006)[21] and Finckh et al. (2009)[23] overcame this limitation by developing a time-to-event model.

The six older studies evaluating cDMARDs in recent-onset RA were less likely to meet the Drummond checklist for assessing the quality of the study.[24,26,29–31] Only Maetzel et al. (2002) fully met the Drummond criteria.[26] The other studies in general did not have a long enough time horizon to fully capture future costs and benefits,[24,29–31,33] and did not report a fully incremental analysis between alternatives.[24,29,33] Probabilistic Sensitivity Analysis was not commonly performed: however, if detailed and comprehensive scenario and one-way analyses were performed, then it was considered that this was an appropriate level of testing for uncertainty.

Of the eight newer studies, five fully met the Drummond criteria.[21–23,32,34] Kobelt et al. (2011),[25] Schipper et al. (2011),[27] and Spalding et al. (2006)[28] did not clearly detail the evidence to establish the programme's effectiveness, and the latter two studies did not report fully incremental results.

4.4 Health economic results in recent-onset RA

Seven studies (50%) evaluated the economic impact of cDMARDs in patients with recent-onset RA.[21–23,25,27,28,34,35] Three of these studies evaluated combination cDMARD strategies, and all three found that a combination of cDMARDs dominated monotherapy cDMARDs.[29,31,32] Of the remaining four studies, three evaluated leflunomide monotherapy. Maetzel et al. (2002) estimated an incremental cost-effectiveness ratio (ICER) for leflunomide of $Can71k per QALY compared with a cDMARD sequence.[26] Kobelt et al. (2002)

concluded that leflunomide can dominate or is dominated by sulfasalazine and methotrexate, depending on the clinical evidence used to derive effectiveness.[30] Schadlich et al. (2005) estimated that adding leflunomide to a cDMARD sequence generated additional QALYs, with an ICER of €8k per QALY. Hartman et al. (2004) estimated that, adjunct to methotrexate, folic acid was dominated by placebo, and folinic acid dominated placebo.[24]

In the seven studies (50%) evaluating the economic impact of bDMARDs in patients with recent-onset RA, the general conclusion was that bDMARDs added both incremental costs and incremental benefits to cDMARD comparators.[21–23,25,27,28,34] Chen et al. (2006),[21] Schipper et al. (2011),[27] Spalding et al. (2006),[28] and van den Hout et al. (2009)[34] concluded that the ICERs comparing bDMARDs to cDMARDs are likely to be too high for decision-makers to approve. Only Davies et al. (2009),[22] with an ICER of $47k per QALY for adalimumab plus methotrexate versus cDMARDs, and Kobelt et al. (2011),[25] with an ICER of €13k per QALY for etanercept plus methotrexate versus methotrexate, are potentially within the UK threshold for being cost-effective.[36] Both analyses are for countries (US and Sweden respectively) where cost-effectiveness thresholds are not established with health resource allocation decision-making. Finckh et al. (2009) estimated that bDMARDs would be dominated by cDMARDs in recent-onset RA.[23]

Of the 14 studies, six (43%) reported that the results were robust when undertaking sensitivity analyses.[27,29–31,33,35] It was not possible to clearly identify what criteria were used to suggest the results were robust. It was also not possible to check whether rigorous testing had been performed. Eight studies reported significant uncertainty,[21–26,28,32,34,37] with four studies (29%) reporting specific model parameters which lead to significant sensitivity in the economic model. These were the progression rate of HAQ whilst on treatment,[21,22] the mapping algorithm from HAQ to utility,[22] the initial effectiveness,[21] the withdrawal rate for cDMARDs,[22] and the initial change in HAQ score after a treatment response.[28]

5. Critical appraisal of studies in established RA

This section presents a critical appraisal of 42 studies providing economic evidence for treatments of established RA.[38–79]

5.1 Scope of the economic evaluations of disease-modifying therapies in established RA

The summary details for all of the established RA economic evaluations are presented in Table 2. 29 of the 42 studies (69%) were CUA's, with effects quantified as QALYs.[39–43,45–47,51–56,58–62,64–66,73–79] Nine studies (21%) were cost-effectiveness analyses (CEA's),[38,44,48–50,68,70–72] with four using low disease activity score (LDAS) or remission as the unit of effect,[44,50,70,71] two with ACR70 weighted response,[48,49] and one study using per patient improved,[38] one HAQ improvement,[68] and one DAS improvement.[72] Two studies (5%) were cost consequence analyses (CCA's),[57,63] and two studies (5%) were cost minimisation analyses (CMA's).[67,69]

The studies were diverse in their treatments considerations and only four (9%) studies were exclusively for cDMARDs.[38,63,68,72] This probably reflects the development of bDMARD therapies in the last 15 years,

and their relatively high prices requiring a formal economic evaluation to determine if they offer value for money for use in patients with established RA.

In 14 (33%) of the 42 studies, the disease severity in the patient population being evaluated was not clearly reported.[38,41,46,48,49,51,58,59,64,67,68,72,74,77] 11 (26%) studies were reported as being in an active RA patient population.[61–63,65,66,69,78,79] Four (9%) of studies were in a severe/aggressive RA patient population,[40,52,54,60] leaving 13 (31%) studies in a moderate-severe RA patient population.[39,42,44,47,50,53,57,70,71,73,75,76,80]

Only 19 (45%) of the studies had a lifelong time horizon for the economic evaluation.[39–41,45,46,51,53–56,62,64,66,73–77,79] All of these studies used decision-analytic modelling methods. None of the cDMARD exclusive studies in established RA had a lifelong time horizon. 17 (40%) studies had a time horizon of no more than two years.[38,42–44,47–50,57,58,63,67–72]

36 (86%) of the 42 studies used decision analytic modelling methods to determine the expected costs and QALYs.[38–41,44–57,59–62,64–67,69–71,73–79] These include prospective studies with a model to extrapolate estimates into the longer-term. Of the six remaining studies, five were observational studies,[42,58,68,72,80] and one was an economic evaluation alongside a clinical trial.[63] None of these six studies had a time horizon longer than two years.

5.2 Downstream costs and effects in established RA

In the 19 studies with a lifelong time horizon for the economic evaluation, 13 (68%) explicitly modelled a downstream sequence of treatments.[39,41,45,46,51,53–56,62,64,74,81] None of these studies attempted to estimate the optimal sequence of treatments from the available treatment set.

Bansback et al. (2005) evaluated bDMARDs with or without adjunct methotrexate versus cDMARDs in patients who had already failed two previous cDMARDs.[39] The downstream cDMARD sequence was explicitly modelled, but the sequence was fixed for all comparisons. Hallinen et al. (2010) compared alternative sequences of bDMARDs after failure on one bDMARD.[54]

Jobanputra et al. (2002),[55] and Barton et al. (2004),[41] evaluated etanercept and infliximab in a cDMARD sequence. Etanercept and infliximab were evaluated in three different positions in a sequence of 10 active therapies. The same decision analytic model was used by Clark et al. (2004) to evaluate anakinra in alternative positions in a cDMARD sequence,[51] and by Malottki et al. (2011) to evaluate bDMARDs after failure on a previous bDMARD.[64]

Brennan et al. (2004) evaluated etanercept in a cDMARD sequence. Etanercept was only evaluated in one position, after two cDMARDs had failed,[46] however alternative downstream sequences were modelled in scenario analyses. This was the same for a later evaluation by Brennan et al. (2007) comparing TNFα's as a class to a cDMARD sequence.[45] Tanno et al. (2006) evaluated etanercept in a sequence of three cDMARDs over a patient's lifetime, after failure on bucillamine.[74] In the latter case, the downstream sequence is likely to be too short and omitted other cDMARD options and sequential bDMARD use for this patient population.

Diamantopoulos et al. (2012) compared alternative positions of tocilizumab in a bDMARD naïve and experienced population.[53] Kielhorn et al. (2008) evaluated the introduction of rituximab plus methotrexate after people had failed on two previous bDMARDs.[56] The downstream sequence, or position of rituximab plus methotrexate, was not altered. Lindgren et al.(2009) evaluated the introduction of rituximab after failure on one previous bDMARD.[62] The subsequent sequence of treatments was not altered. Merkesdal et al. (2010) evaluated the introduction of rituximab after failure on one previous bDMARD.[66] The subsequent sequence of cDMARDs was not altered, and no comparison to other bDMARDs was made.

Six studies (72%) had a lifelong time horizon but did not explicitly model the downstream treatments.[40,73,75–77,79] Barbieri et al (2005) simulated HAQ states with associated costs and utilities.[40] Soini et al. (2012) modelled progression to best supportive care, but did not clearly report how costs and health-related quality of life were estimated.[73] Vera-Llonch et al. (2008) used the same model for two analyses, and after treatment withdrawal moved onto a linear extrapolation of HAQ with mapped estimates of costs and utilities.[75,76] Wailoo et al. (2008) also extrapolated HAQ after treatment withdrawal.[77] Wong et al. (2002) estimated future costs and health effects by simulating a worsening of HAQ score via movement of the modelled cohort through Markov health states.[79]

23 of the 42 studies (55%) in established RA did not have a lifelong time horizon. Of these, only six (26%) explicitly modelled a downstream sequence of treatments.[44,50,52,70,71,78] The time horizon for these studies was no longer than five years, and only Coyle et al. (2006) considered more than one downstream treatment in the sequence (the other five modelling only a switch onto one other active therapy).[52]

17 studies remain with a truncated time horizon and no explicit inclusion of long-term costs and effects[26,38,42,43,47–49,57–61,65,67–69,72]. The justification for this omission of long-term future costs and effects is not clear in any of the studies. Five studies are observational analyses,[42,58,68,72,80] and one is an evaluation alongside a trial,[63] and therefore long-term modelling may not have been the primary research objective.

5.3 Decision-analytic modelling methods in established RA

As already mentioned, 36 (86%) of the 42 studies used decision analytic modelling methods to determine the expected costs and QALYs.[38–41,44–57,59–62,64–67,69–71,73–79] Five (14%) of the 36 models were a decision tree,[38,47–49,70] nine (25%) were cohort Markov models,[40,52,59–61,65,74,78,79] and 16 (44%) were individual patient models.[39,41,45,46,51,53–56,62,64,66,73,75–77] For the remaining six (17%) studies, the method of decision-analytic modelling was unclear.[44,50,57,67,69,71]

Of the five decision tree models,[38,47–49,70] none had a time horizon of over two years, and only Russell et al. (2009) considered sequential use of therapies.[70] Moving onto a second therapy was determined by either achieving LDAS or remission, and the evidence for this was not clearly reported.

The nine Markov models were also limited in considering the costs and effects of future treatments.[40,52,59–61,65,74,78,79] Only five met the Drummond criteria,[59,61,65,74,79] only three had a lifelong time horizon,[40,74,79] and only three considered sequential use of treatments.[52,74,78]

The 16 individual level simulations all had a lifelong time horizon.[39,41,45,46,51,53–56,62,64,66,73,75–77] 12 of these studies also considered sequential use of therapies in patients with established RA.[39,41,45,46,51,53,54,56,62,64,66] All 12 determined a treatment switch by either a short-term lack of response, or a long-term withdrawal due to a loss of efficacy or an adverse event. Initial response was modelled using an ACR response mapped to a HAQ improvement in six models.[39,46,53,54,56,66] Brennan et al. (2007) modelled initial treatment response using the European League Against Rheumatism (EULAR) response categories and mapping the response to EQ-5D (or SF-6D) via a multivariate regression.[45]

Only 17 of the 42 (40%) met the Drummond checklist for assessing the quality of the study:[41,45,46,51,54,56,59,61,64–66,74–77,79] Five of nine Markov Models;[59,61,65,74,79] and 12 of 16 individual level simulations.[41,45,46,51,54,56,62,64,66,75–77] The most common reasons for not meeting the Drummond criteria were: not providing a comprehensive description of the competing alternatives;[73,78] not providing evidence that the programme's effectiveness had been established;[48,55,67,69] not including all important and relevant costs and consequences;[44,48,50,57,69,78] not measuring costs and consequences appropriately;[44,50] not undertaking a fully incremental analysis;[38,39,44,50,52,53,57,60,67,69–71] not allowing for uncertainty;[40,47–49,69,71] and not including all issues of interest.[38–40,44,48,50,52,53,55,57,60,67,69–71]

5.4 Health economic results in established RA

The headline health economic results are provided for each study in Table 2. None of the studies looked to identify the optimal sequence of treatments from the treatment set included in the analysis.

Four of the 42 studies (10%) were exclusively for cDMARDs in patients with established RA.[38,63,68,72] Maetzel et al (2002) observed in a one year economic evaluation alongside a clinical trial that methotrexate dominated leflunomide and placebo.[63] Osiri et al (2007) concluded that methotrexate plus antimalarials dominated antimalarials, and non-methotrexate strategies were unlikely to be cost effective.[68] Shini et al. (2010) performed a CEA with change in HAQ as the unit of health benefit.[72] Their study suggested that hydroxychloroquine is the most cost effective monotherapy cDMARD strategy, with methotrexate plus hydroxychloroquine the most cost effective combination strategy. Anis et al. (1996) estimated an ICER of cyclosporine therapy of $1k per patient improved compared to placebo.[38]

19 studies (45%) were non-sequential evaluations of bDMARDs in patients with established RA.[40,42,43,47–49,57,60,61,65,67,69,73,75–77,79] In general, the studies found that bDMARDs were more effective but also more costly compared to cDMARDs in patients with established disease. This conclusion was consistent across all studies, irrespective of country, patient population or method of evaluation. Six of the 19 studies were decision-analytic models with a lifelong time horizon.[40,73,75–77,79] Barbieri et al. (2005)[40] and Wong et al. (2002)[79] estimated an ICER for infliximab plus methotrexate versus methotrexate of £33k and £30k per QALY, respectively. Likewise, two analyses performed by Vera-Llonch et al. (2008) estimated an ICER for abatacept plus methotrexate versus methotrexate of $43k per QALY and $45k per QALY, in a TNFα naïve[76] and TNFα experienced[75] patient population, respectively.

19 studies (45%) were evaluations of alternative sequences of bDMARDs in patients with established RA.[39,41,44–46,50–56,62,64,66,70,71,74,78] 13 of these studies had a lifelong time horizon, and as before these studies found sequential bDMARD use to be more effective but also more costly.[39,41,45,46,51,53–56,62,64,66,74]

Four studies evaluated the introduction of rituximab into a sequence of DMARDs. Hallinen et al. (2010),[54] Lindgren et al. (2009),[62] and Merkesdal et al. (2010)[66] concluded that rituximab was cost-effective after TNFα failure compared to TNFα's. Kielhorn et al. (2008) found that rituximab after two TNFα failures was cost-effective.[56] None of the studies considered the optimal position of rituximab, comparing rituximab after one or two TNFα failures.

Of the nine remaining studies, nearly all were consistent in concluding that bDMARDs were likely to be cost effective. The studies by Barton et al. (2004)[41] and Jobanputra et al. (2002)[55] were the only studies to conclude that, after two cDMARDs, bDMARDs were unlikely to be cost effective compared to further cDMARD treatment.

There were six studies with an explicitly modelled sequence of downstream treatments, but with a truncated time horizon.[44,50,52,70,71,78] These studies reported that bDMARDs were less likely to be cost effective. The truncated time horizon may therefore omit important downstream health benefits from bDMARDs, such as delayed joint erosion or disease progression.

22 of 42 (52%) of studies reported that the results were robust when undertaking sensitivity analyses.[40,41,44,48,50,52–54,56–59,61,62,64,67,69,71,75,76,78,79] As with the similar conclusion from the recent-onset RA population, it was not clear what criteria had been used to suggest that the results were robust, and whether rigorous enough testing had been performed. Eight studies (19%) reported significant uncertainty,[39,45–47,49,55,65,73] with six studies (14%) reporting specific model parameters which lead to significant sensitivity in the economic model. These were: the baseline age in the model;[39] the standardised mortality ratios;[39] the algorithm to estimate health related quality of life;,[39,45,65] the rate of disease progression;[45,46] discount rates;[45] treatment response rates;[47] and cost parameters.[49]

6. Discussion

A number of key themes have been identified from this systematic review of economic evaluations of sequential disease modifying therapies for rheumatoid arthritis.

Firstly, the review highlights the significant number of decisions that potentially wait to be informed in the decision space within RA. 14 economic evaluations were identified of therapies within a recent-onset RA population, and 42 within an established RA population. Evaluations were undertaken when people had no prior treatment, up to patients having had cDMARDs and two bDMARDs. There were several potential positions for each DMARD therapy, and the review identified approximately 30 discrete treatments. Therefore the decision

space on a very crude level is every potential sequence constructed from that set of 30 treatments[1]. Understandably, the vast decision space and huge number of potential comparators led to no study attempting to determine the optimal sequence of therapies. The evaluation by Chen et al. (2006) represents the only attempt from 57 evaluations to determine whether bDMARDs should be used in recent-onset or established RA.[21] However the evaluation only represents a small subset of the available sequences. The review has identified a significant number of constrained or pair-wise evaluations, the majority of which did not conduct a fully incremental analysis or discuss the possibility of alternative positions other than the primary analysis. This is not particularly surprising, because each study was undertaken for its own particular decision-making context. The heterogeneity in terms of comparators, sequences and methodology reflect both local/national variation and also the context in which health economic evaluation is conducted. A clear finding was that combination cDMARDs have an important role in the treatment of RA, and appear to be dominant or cost-effective at early positions in a sequence.

Secondly, modelling methodology was associated with the quality of the study and the ability to evaluate alternative sequences. Models with a lifelong time horizon were more likely to be an individual patient simulation, and Markov and decision tree models were less likely to evaluate sequential treatments. In all studies, the quality of reporting about the impact of future treatments on costs and health benefits was varied. However, in several sensitivity analyses the long term progression of disease was shown to be a key parameter for model sensitivity. The mapping from HAQ to utility was also a source of uncertainty, which is a methodological challenge detailed in other published studies.[82–84]

Finally, when downstream treatments were explicitly modelled, the evidence used to parameterise this part of the model was from disparate sources, and also poorly reported. Evidence used was often referred to rather than explicitly stated. In several evaluations assumptions of equal efficacy between treatments, or potential treatment decrements for later positioning within a sequence, was assumed when direct evidence was not identified. However the quantitative or qualitative evidence to support these assumptions was not provided. The assumptions lead to significant uncertainties in the evaluations, and also highlighted that when cDMARDs or bDMARDs can largely be considered a class, with similar costs and health effects, small assumptions can have a significant impact on a treatment's cost-effectiveness. Therefore it is important to identify and synthesise all relevant evidence to inform models, not just at the divergence point, but also throughout the complete model pathway. On the balance of all of these issues, it is not clear if failure to address the methodological issues regarding sequence modelling has inaccurate results of evaluations in a particular direction for specific treatments

A recent systematic review by Sullivan et al. has also reviewed the economic evidence of sequencing bDMARDs in RA.[85] The review had a different perspective, and focussed on purely the cost-effectiveness evidence identified. As with this review, they found that the evidence was uncertain and unclear, and recommendations were hard to draw. Our review builds upon this by focussing on the methodological and evidence base issues which remain unresolved with an intention to improve future economic evaluations.

[1] 30! = 265,252,859,812,191,058,636,308,480,000,000. If each sequence took one second to enumerate, it would take over 8 years to evaluate

As with any systematic review, there are limitations that should be considered. The review does not include non-economic evaluations, or purely disease modelling studies. Some studies which modelled sequences of treatments may have been omitted if no comparison between alternative strategies was presented. Secondly, there were some aspects of the data extraction which relied on a certain level of subjectivity. Where possible, checkbox choices and the Drummond checklist were used to ensure bias was minimised. However, when considering particular modelling methodologies the subjective decisions were necessary by the reviewer. To minimise bias, the reviewer relied on what was reported by the author as fact. Identified systematic reviews of economic evaluations in RA were cross-checked when data extraction overlapped. Also, data regarding the 'rebound' assumption made in the model when patients withdraw from treatment were not extracted. The rebound assumption is contentious and un-evidenced, and sequential models rely on an assumption every time a treatment is switched.[86,87] Further research is required for this issue. Finally, manufacturer's submissions to organisations such as NICE were not included, because full text versions of their reports are not publically available.

The review has highlighted issues when trying to undertake an economic evaluation of sequential therapies. These present both methodological challenges when developing models, and also decision-making issues when looking to develop guidance based on cost-effectiveness evidence. In particular, the factorial rate of growth in the number of comparator sequences becomes unfeasible for standard decision-analytic models. Enumerating every possible sequence is not likely to be practical as the computational time and evidence requirements would be enormous. Heuristic methods from the field of operational research of searching for a near-optimal sequence may be a potential solution, as well as methods to improve the tractability of developed model. Future reviewing and analysis will be undertaken to identify methodological solutions, with the aim of developing a methodological framework for the economic evaluation of sequential therapies is chronic conditions. While the problem is significant in RA, there are other conditions where this framework may be relevant, including multiple sclerosis, depression, psoriatic arthritis and Crohn's disease. Any further research should be generalisable across these conditions.[88,89]

7. Conclusions

The review has identified 57 unique economic evaluations of disease modifying therapies for people with RA. Almost half modelled sequences of DMARDs, however none of the identified studies have considered identifying the most cost effective sequence from the full treatment set available. This has therefore led to clinical guidance being developed without the required economic evidence being available to ensure that health resource allocation decisions are fully informed, and therefore an optimal allocation of resources identified. 24 (42%) models have been developed that consider a lifelong time horizon, and 25 (44%) had a downstream treatment sequence. In these studies, evidence gaps have were identified. These include the efficacy of treatments in downstream positions, and the long term impact of treatments on costs and health related quality of life in the future. The review has identified that methods have not been consistently applied, which has led to varied estimates of cost-effectiveness and uncertainty with respect to the most appropriate analyses to address

particular decision questions. Research is required to develop a methodological framework for the economic evaluation of sequential therapies in chronic conditions.

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References

1. Symmons D. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology [Internet]. 2002 [cited 2012 May 11];41:793–800. Available from: http://rheumatology.oxfordjournals.org/cgi/content/abstract/41/7/793

2. Wolfe F, Michaud K. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum. [Internet]. 2003 [cited 2013 Aug 15]; Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.11024/full

3. Burton W, Morrison A, Maclean R, Ruderman E. Systematic review of studies of productivity loss due to rheumatoid arthritis. Occup. Med. (Lond). [Internet]. 2006 [cited 2013 Aug 9];56:18–27. Available from: http://occmed.oxfordjournals.org/content/56/1/18.short

4. Kobelt G, Jönsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis Rheum. [Internet]. 2002 [cited 2013 Aug 29];46:2310–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12355478

5. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previo. Arthritis Rheum. [Internet]. 2006 [cited 2013 Aug 15];54:26–37. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.21519/full

6. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum. [Internet]. 2000 [cited 2013 Aug 15];43:2383–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11083258

7. St Clair EW, van der Heijde DMFM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. [Internet]. 2004 [cited 2013 Aug 8];50:3432–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15529377

8. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N. Engl. J. Med. [Internet]. 2000 [cited 2013 Aug 15];343:1594–602. Available from: http://www.nejm.org/doi/full/10.1056/nejm200011303432202

9. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N. Engl. J. Med. [Internet]. 2000 [cited 2013 Aug 15];343:1586–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11096165

10. Maini R, Clair ES, Breedveld F, Furst D. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a. Lancet [Internet]. 1999 [cited 2013 Aug 15]; Available from: http://www.sciencedirect.com/science/article/pii/S0140673699052460

11. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N. Engl. J. Med. [Internet]. 1999 [cited 2013 Aug 9];340:253–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9920948

12. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. [Internet]. 2003 [cited 2013 Aug 14];48:35–45. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.10697/full

13. Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J. Rheumatol. [Internet]. 2006 [cited 2013 Aug 15];33:2398–408. Available from: http://www.jrheum.org/content/33/12/2398.short

14. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ [Internet]. 2009 [cited 2013 Aug 9];181:787–96. Available from: http://www.cmaj.ca/content/181/11/787.short

15. Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy [Internet]. 2010 [cited 2013 Aug 15];30:339–53. Available from: http://onlinelibrary.wiley.com/doi/10.1592/phco.30.4.339/abstract

16. National Institute for Health and Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (TA130). 2007.

17. Brennan A, Akehurst R. Modelling in health economic evaluation. Pharmacoeconomics [Internet]. 2000 [cited 2012 Jul 16]; Available from: http://www.med.mcgill.ca/epidemiology/courses/EPIB654/Summer2010/Modeling/Brennan PharmEco00.pdf

18. Bansback N, Ara R, Karnon J, Anis A. Economic evaluations in rheumatoid arthritis: a critical review of measures used to define health States. Pharmacoeconomics [Internet]. 2008 [cited 2013 Jan 16];26:395–408. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18429656

19. National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults. London; 2009.

20. Drummond MF, Sculpher MJ, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes [Internet]. Oxford University Press; 2005 [cited 2012 May 31]. p. 379. Available from: http://books.google.com/books?hl=en&lr=&id=xyPLJIiEn7cC&pgis=1

21. Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. [Internet]. Health Technol. Assess. England: West Midlands Health Technology Assessment Collaboration (WMHTAC), Department of Public Health and Epidemiology, University of Birmingham, UK.; 2006. p. iii–229. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17049139

22. Davies A, Cifaldi MA, Segurado OG, Weisman MH. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. [Internet]. J. Rheumatol. Canada: United BioSource Corporation, London, UK. andy.davies@oxfordoutcomes.com; 2009. p. 16–26. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19012363

23. Finckh A, Bansback N, Marra CA, Anis AH, Michaud K, Lubin S, et al. Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost-effectiveness analysis. [Internet]. Ann. Intern. Med. United States: Division of Rheumatology, Department of Internal Medicine, University of Geneva, Geneva, Switzerland.; 2009. p. 612–21. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19884622

24. Hartman M, van Ede A, Severens JL, Laan RFJM, van de Putte L, van der Wilt GJ. Economic evaluation of folate supplementation during methotrexate treatment in rheumatoid arthritis. [Internet]. J. Rheumatol. Canada: Department of Medical Technology Assessment, University Medical Centre, Nijmegen, The Netherlands. M.Moret@mta.umcn.nl; 2004. p. 902–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15124248

25. Kobelt G, Lekander I, Lang A, Raffeiner B, Botsios C, Geborek P. Cost-effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment. [Internet]. Int. J. Technol. Assess.

Health Care. England: Lund University and European Health Economics.; 2011. p. 193–200. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21736857

26. Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Cost effectiveness of adding leflunomide to a 5-year strategy of conventional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. [Internet]. Arthritis Rheum. United States: University Health Network Research Institute, Toronto, Ontario, Canada. maetzel@uhnres.utoronto.ca; 2002. p. 655–61. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12522841

27. Schipper LG, Kievit W, den Broeder AA, van der Laar MA, Adang EMM, Fransen J, et al. Treatment strategies aiming at remission in early rheumatoid arthritis patients: starting with methotrexate monotherapy is cost-effective. [Internet]. Rheumatology (Oxford). England: Department of Rheumatology, Radboud University Nijmegen Medical Centre, Sint Maartenskliniek Nijmegen, Nijmegen, The Netherlands. lschipper@reuma.umcn.nl; 2011. p. 1320–30. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21371999

28. Spalding JR, Hay J. Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. [Internet]. Pharmacoeconomics. New Zealand: Astellas Pharma US, Deerfield, Illinois, USA.; 2006. p. 1221–32. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17129076

29. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-effectiveness and cost-utility of combination therapy in early rheumatoid arthritis: randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone. COBRA Trial Group. Combinatietherapie Bij Reumat [Internet]. Br. J. Rheumatol. ENGLAND: Department of Internal Medicine and Rheumatology, Maastricht University Hospital, The Netherlands.; 1998. p. 1102–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=9825750

30. Kobelt G, Lindgren P, Young A. Modelling the costs and effects of leflunomide in rheumatoid arthritis. Eur. J. Health Econ. [Internet]. 2002;3:180–7. Available from: MEDLINE:15609143

31. Korthals-de Bos IBC, van Tulder MW, Boers M, Verhoeven AC, Ader HJ, Bibo J, et al. Indirect and total costs of early rheumatoid arthritis: A randomized comparison of combined step-down prednisolone, methotrexate and sulfasalazine with sulfasalazine alone. Arthritis Rheum. [Internet]. 2001;44:S313–S313. Available from: WOS:000172495901623

32. Tosh JC, Wailoo AJ, Scott DL, Deighton CM. Cost-effectiveness of combination nonbiologic disease-modifying antirheumatic drug strategies in patients with early rheumatoid arthritis. J. Rheumatol. [Internet]. 2011;38(8):1593–600. Available from: http://www.jrheum.org/content/38/8/1593.abstract

33. Schädlich PK, Zeidler H, Zink A, Gromnica-Ihle E, Schneider M, Straub C, et al. Modelling cost effectiveness and cost utility of sequential DMARD therapy including leflunomide for rheumatoid arthritis in Germany: II. The contribution of leflunomide to efficiency. Pharmacoeconomics [Internet]. 2005 [cited 2013 Jan 18];23:395–420. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15853438

34. Van den Hout WB, Goekoop-Ruiterman YPM, Allaart CF, de Vries-Bouwstra JK, Hazes JMM, Kerstens PJSM, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. Arthritis Care Res. [Internet]. United States: Department of Medical Decision Making, Leiden University Medical Center, Leiden, The Netherlands. Hout@lumc.nl; 2009;61:291–9. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2010215566&site=ehost-live

35. Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M. Management of rheumatoid arthritis: summary of NICE guidance. BMJ [Internet]. 2009 [cited 2012 May 11];338:b702. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3266846&tool=pmcentrez&rendertype=abstract

36. National Insitute for Health and Care Excellence. Guide to the methods of technology appraisal [Internet]. 2013. Available from: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf

37. Kavanaugh A, Heudebert G, Cush J, Jain R. Cost evaluation of novel therapeutics in rheumatoid arthritis (CENTRA): A decision analysis model. Semin. Arthritis Rheum. [Internet]. 1996;25:297–307. Available from: WOS:A1996UE92700002

38. Anis AH, Tugwell PX, Wells GA, Stewart DG. A cost effectiveness analysis of cyclosporine in rheumatoid arthritis. [Internet]. J. Rheumatol. CANADA: Health Research Centre, St. Paul's Hospital, Vancouver, Ottawa, Canada.; 1996. p. 609–16. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=8730113

39. Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. [Internet]. Ann. Rheum. Dis. England: Health Economics and Decision Science, ScHARR, University of Sheffield, Regent Court, 40 Regent Street, Sheffield S1 4DA UK. n.j.bansback@sheffield.ac.uk; 2005. p. 995–1002. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15550533

40. Barbieri M, Wong JB, Drummond M. The cost effectiveness of infliximab for severe treatment-resistant rheumatoid arthritis in the UK. [Internet]. Pharmacoeconomics. New Zealand: Universitat Pompeu Fabra, Barcelona, Spain.; 2005. p. 607–18. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15960556

41. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol. Assess. (Rockv). [Internet]. 2004;8(11):1–104. Available from: http://www.hta.ac.uk/1296

42. Benucci M, Gobbi F, Sabadini L, Saviola G, Baiardi P, Manfredi M. The Economic Burden of Biological Therapy in Rheumatoid Arthritis in Clinical Practice: Cost-Effectiveness Analysis of Sub-Cutaneous Anti-Tnf Alpha Treatment in Italian Patients. Int. J. Immunopathol. Pharmacol. [Internet]. 2009;22:1147–52. Available from: WOS:000274293700034

43. Benucci M, Saviola G, Baiardi P, Manfredi M. Cost-effectiveness treatment with Rituximab in patients with rheumatoid arthritis in real life. [Internet]. Rheumatol. Int. Germany: Rheumatology Unit, Department of Internal Medicine, Ospedale di S. Giovanni di Dio, Azienda Sanitaria di Firenze, Via Torregalli 3, 50143 Florence, Italy. maubenucci@tiscali.it; 2011. p. 1465–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20473760

44. Beresniak A, Ariza-Ariza R, Garcia-Llorente JF, Ramirez-Arellano A, Dupont D. Modelling cost-effectiveness of biologic treatments based on disease activity scores for the management of rheumatoid arthritis in Spain. Int. J. Inflam. [Internet]. 2011;2011:727634. Available from: MEDLINE:21785694

45. Brennan A, Bansback N, Nixon R, Madan J, Harrison M, Watson K, et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. [Internet]. Rheumatology (Oxford). England: Health Economics and Decision Science, School of Health and Related Research (ScHARR), The University of Sheffield, UK. a.brennan@sheffield.ac.uk; 2007. p. 1345–54. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17562686

46. Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. [Internet]. Rheumatology (Oxford). England: Operational Research, School of Health and Related Research, University of Sheffield, Sheffield, South Yorkshire, UK. A.Brennan@Sheffield.ac.uk; 2004. p. 62–72. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12890861

47. Chiou C-F, Choi J, Reyes CM. Cost-effectiveness analysis of biological treatments for rheumatoid arthritis. Expert Rev. Pharmacoeconomics Outcomes Res. 2004;4:June.

48. Choi HK, Seeger JD, Kuntz KM. A cost-effectiveness analysis of treatment options for patients with methotrexate-resistant rheumatoid arthritis. [Internet]. Arthritis Rheum. UNITED STATES: Massachusetts

General Hospital, Boston 02114, USA.; 2000. p. 2316–27. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11037892

49. Choi HK, Seeger JD, Kuntz KM. A cost effectiveness analysis of treatment options for methotrexate-naive rheumatoid arthritis. [Internet]. J. Rheumatol. Canada: Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston 02114, USA. HCHOI@PARTNERS.ORG; 2002. p. 1156–65. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12064828

50. Cimmino MA, Leardini G, Salaffi F, Intorcia M, Bellatreccia A, Dupont D, et al. Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in Italy: a modelling approach. [Internet]. Clin. Exp. Rheumatol. Italy: Department of Internal Medicine, University of Genoa, Genoa, Italy.; 2011. p. 633–41. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21813056

51. Clark W, Jobanputra P, Barton P, Burls A. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. [Internet]. Health Technol. Assess. England: Medicines Evaluation Unit, Department of Medicines Management, Keele University, UK.; 2004. p. iii–105. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15130461

52. Coyle D, Judd M, Blumenauer B, Cranney A, Maetzel A, Tugwell P, et al. Infliximab and etanercept in patients with rheumatoid arthritis: a systematic review and economic evaluation (Technology Report no 64). Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2006.

53. Diamantopoulos A, Benucci M, Capri S, Berger W, Wintfeld N, Giuliani G, et al. Economic evaluation of tocilizumab combination in the treatment of moderate-to-severe rheumatoid arthritis in Italy. J. Med. Econ. 2012;15:June.

54. Hallinen TA, Soini EJO, Eklund K, Puolakka K. Cost-utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. [Internet]. Rheumatology (Oxford). England: ESiOR Oy, Kuopio, Finland. taru.hallinen@esior.fi; 2010. p. 767–77. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20100793

55. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. [Internet]. Health Technol. Assess. England: Department of Public Health and Epidemiology, University of Birmingham, UK.; 2002. p. 1–110. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12387732

56. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. [Internet]. Curr. Med. Res. Opin. England: F. Hoffmann La-Roche Ltd, Basel, Switzerland. adrian.kielhorn@roche.com; 2008. p. 2639–50. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18687164

57. Kievit W, Fransen J, Adang EM, Kuper HH, Jansen TL, De Gendt CMA, et al. Evaluating guidelines on continuation of anti-tumour necrosis factor treatment after 3 months: clinical effectiveness and costs of observed care and different alternative strategies. [Internet]. Ann. Rheum. Dis. England: Department of Rheumatology, Radboud University Nijmegen Medical Centre, The Netherlands. w.kievit@reuma.umcn.nl; 2009. p. 844–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18625616

58. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. [Internet]. Ann. Rheum. Dis. England: Karolinska Institute, Huddinge Hospital, Stockholm, Sweden. gisela.kobelt@he-europa.com; 2004. p. 4–10. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14672883

59. Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. [Internet]. Rheumatology (Oxford). England: HDI France, Speracedes, France. gisela.kobelt@easynet.fr; 2003. p. 326–35. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12595631

60. Kobelt G, Lindgren P, Singh A, Klareskog L. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. [Internet]. Ann. Rheum. Dis. England: European Health Economics SAS, 492 chemin des Laurens, F-06530 Speracedes, France. gisela.kobelt@he-europe.com; 2005. p. 1174–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15708879

61. Lekander I, Borgstrom F, Svarvar P, Ljung T, Carli C, van Vollenhoven RF. Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. [Internet]. Int. J. Technol. Assess. Health Care. England: i3 Innovus and MMC, LIME, Stockholm, Sweden. ingrid.lekander@i3innovus.com; 2010. p. 54–61. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20059781

62. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. [Internet]. Int. J. Technol. Assess. Health Care. England: i3/innovus, Klarabergsviadukten 90D, SE-111 64 Stockholm, Sweden. Peter.Lindgren@3innovus.com; 2009. p. 181–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19331709

63. Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Economic comparison of leflunomide and methotrexate in patients with rheumatoid arthritis: an evaluation based on a 1-year randomised controlled trial. [Internet]. Pharmacoeconomics. New Zealand: Arthritis and Immune Disorder Research Centre, University Health Network, Toronto, Ontario, Canada. maetzel@uhnres.utoronto.ca; 2002. p. 61–70. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11817993

64. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. [Internet]. Health Technol. Assess. England: West Midlands Health Technology Assessment Collaboration, University of Birmingham, Edgbaston, Birmingham, UK.; 2011. p. 1–278. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21439251

65. Marra CA, Marion SA, Guh DP, Najafzadeh M, Wolfe F, Esdaile JM, et al. Not all "Quality-adjusted life years" are equal. J. Clin. Epidemiol. [Internet]. 2007;60:616–24. Available from: http://www.sciencedirect.com/science/article/pii/S0895435606003593

66. Merkesdal S, Kirchhoff T, Wolka D, Ladinek G, Kielhorn A, Rubbert-Roth A. Cost-effectiveness analysis of rituximab treatment in patients in Germany with rheumatoid arthritis after etanercept-failure. Eur. J. Health Econ. [Internet]. Germany: Division of Clinical Immunology and Rheumatology, Working Group for Health Economics and Clinical Epidemiology, Hannover Medical School, Carl-Neuberg-Strasse 1, OE 6830, 30625, Hannover, Germany. merkesdal.sonja@mh-hannover.de; 2010;11:95–104. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19967426

67. Nuijten MJ, Engelfriet P, Duijn K, Bruijn G, Wierz D, Koopmanschap M. A cost-cost study comparing etanercept with infliximab in rheumatoid arthritis. [Internet]. Pharmacoeconomics. New Zealand: MEDTAP International, Amsterdam, The Netherlands. nuijten@medtap.nl; 2001. p. 1051–64. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11735673

68. Osiri M, Kamolratanakul P, Maetzel A, Tugwell P. Cost effectiveness analysis of disease modifying antirheumatic drugs in rheumatoid arthritis. Rheumatol. Int. [Internet]. 2007;27:1063–9. Available from: WOS:000248813000011

69. Rubio-Terrés C, Domínguez-Gil A. Pharmacoeconomic analysis of the treatment of rheumatoid arthritis with leflunomide in comparison with the combination of infliximab and methotrexate. J. Drug Assess. [Internet]. Pharmacoeconomics Unit, Scientific Dept, Aventis Pharma, SA, Madrid, Spain; 2001;4:39–54. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2003131286&site=ehost-live

70. Russell A, Beresniak A, Bessette L, Haraoui B, Rahman P, Thorne C, et al. Cost-effectiveness modeling of abatacept versus other biologic agents in DMARDS and anti-TNF inadequate responders for the management of moderate to severe rheumatoid arthritis. [Internet]. Clin. Rheumatol. Germany: University of Alberta, Edmonton, Canada.; 2009. p. 403–12. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19089488

71. Saraux A, Gossec L, Goupille P, Bregman B, Boccard E, Dupont D, et al. Cost-effectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in France. [Internet]. Rheumatology (Oxford). England: Department of Rheumatology, Brest University, CHU Brest, Brest, France.; 2010. p. 733–40. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20081224

72. Shini VK, Aboobacker S, Pahuja S, Revikumar KG, Bhasi R. Pharmacoeconomic study of DMARDs in the management of rheumatoid arthritis. Int. J. Pharm. Sci. Rev. Res. 2010;5(3):148–54.

73. Soini EJ, Hallinen TA, Puolakka K, Vihervaara V, Kauppi MJ. Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis. J. Med. Econ. [Internet]. 2012;15:340–51. Available from: MEDLINE:22168785

74. Tanno M, Nakamura I, Ito K, Tanaka H, Ohta H, Kobayashi M, et al. Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis. [Internet]. Mod. Rheumatol. Japan: Department of Rheumatology, Yugawara Kosei-Nenkin Hospital, 438 Miyakami, Yugawara-cho, Ashigarashimo-gun, Kanagawa, 259-0314, Japan. yknb-l12@i-younet.ne.jp; 2006. p. 77–84. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16633926

75. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. [Internet]. J. Rheumatol. Canada: From Policy Analysis Inc., Brookline, MA 02445, USA.; 2008. p. 1745–53. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18634164

76. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. [Internet]. Rheumatology (Oxford). England: Policy Analysis Inc., Brookline, MA 02445, USA.; 2008. p. 535–41. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18356179

77. Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. [Internet]. Arthritis Rheum. United States: Health Economics and Decision Science, ScHARR, University of Sheffield, Sheffield, UK. a.j.wailoo@sheffield.ac.uk; 2008. p. 939–46. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18383356

78. Welsing PMJ, Severens JL, Hartman M, van Riel PLCM, Laan RFJM. Modeling the 5-year cost effectiveness of treatment strategies including tumor necrosis factor-blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands. [Internet]. Arthritis Rheum. United States: University Medical Center Nijmegen, Nijmegen, the Netherlands. P.Welsing@reuma.umcn.nl; 2004. p. 964–73. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15593319

79. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. [Internet]. Am. J. Med. United States: Division of Clinical Decision Making, Department of Medicine, Tupper Research Institute, Tufts-New England Medical Center, Tufts University School of

Medicine, Boston, Massachusetts 02111, USA. jwong@lifespan.org; 2002. p. 400–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12401535

80. Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F. Cost effectiveness analysis of disease-modifying antirheumatic drugs in rheumatoid arthritis. A systematic review literature. Int. J. Rheumatol. [Internet]. 2011 [cited 2013 Jan 16];2011:845496. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3228304&tool=pmcentrez&rendertype=abstract

81. Merkesdal S, Ruof J, Mittendorf T, Zeidler H. Cost-effectiveness of TNF-α-blocking agents in the treatment of rheumatoid arthritis. Expert Opin. Pharmacother. [Internet]. Ashley Publications Ltd London, UK; 2004 [cited 2013 Jan 16];5:1881–6. Available from: http://informahealthcare.com/doi/abs/10.1517/14656566.5.9.1881

82. Harrison MJM, Bansback NJN, Marra CA, Drummond M, Tugwell PS, Boonen A. Valuing health for clinical and economic decisions: directions relevant for rheumatologists. J. Rheumatol. [Internet]. 2011 [cited 2013 Nov 11];38:1770–5. Available from: http://jrheum.org/content/38/8/1770.short

83. Hernández Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). [Internet]. 2013 [cited 2013 Nov 14];52:944–50. Available from: http://rheumatology.oxfordjournals.org/content/early/2013/01/25/rheumatology.kes400.full?keytype=ref&ijkey=IFzd0zj0pdZWOzP

84. Scott DL, Khoshaba B, Choy EH, Kingsley GH. Limited correlation between the Health Assessment Questionnaire (HAQ) and EuroQol in rheumatoid arthritis: questionable validity of deriving quality adjusted life. Ann. Rheum. … [Internet]. 2007 [cited 2013 Nov 9];66:1534–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2111609&tool=pmcentrez&rendertype=abstract

85. Sullivan SD, Alfonso-Cristancho R, Carlson J, Mallya U, Ringold S. Economic consequences of sequencing biologics in rheumatoid arthritis: a systematic review. J. Med. Econ. [Internet]. 2013 [cited 2013 Dec 6];16:391–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23298329

86. Madan J, Ades AE, Welton NJ. An overview of models used in economic analyses of biologic therapies for arthritis--from current diversity to future consensus. Rheumatology [Internet]. 2011 [cited 2013 Nov 15];50:iv10–iv18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859700

87. Tosh J, Brennan A, Wailoo A, Bansback N. The Sheffield rheumatoid arthritis health economic model. Rheumatology (Oxford). [Internet]. 2011 [cited 2012 Feb 22];50 Suppl 4:iv26–31. Available from: http://rheumatology.oxfordjournals.org/cgi/content/abstract/50/suppl_4/iv26

88. Krieger S. Multiple sclerosis therapeutic pipeline: opportunities and challenges. Mt. Sinai J. Med. [Internet]. [cited 2013 Dec 6];78:192–206. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21425264

89. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatry [Internet]. American Psychiatric Association; 2006 [cited 2013 Nov 12];163:1905–17. Available from: http://journals.psychiatryonline.org/article.aspx?volume=163&page=1905

Figure 1: PRISMA Flow Diagram

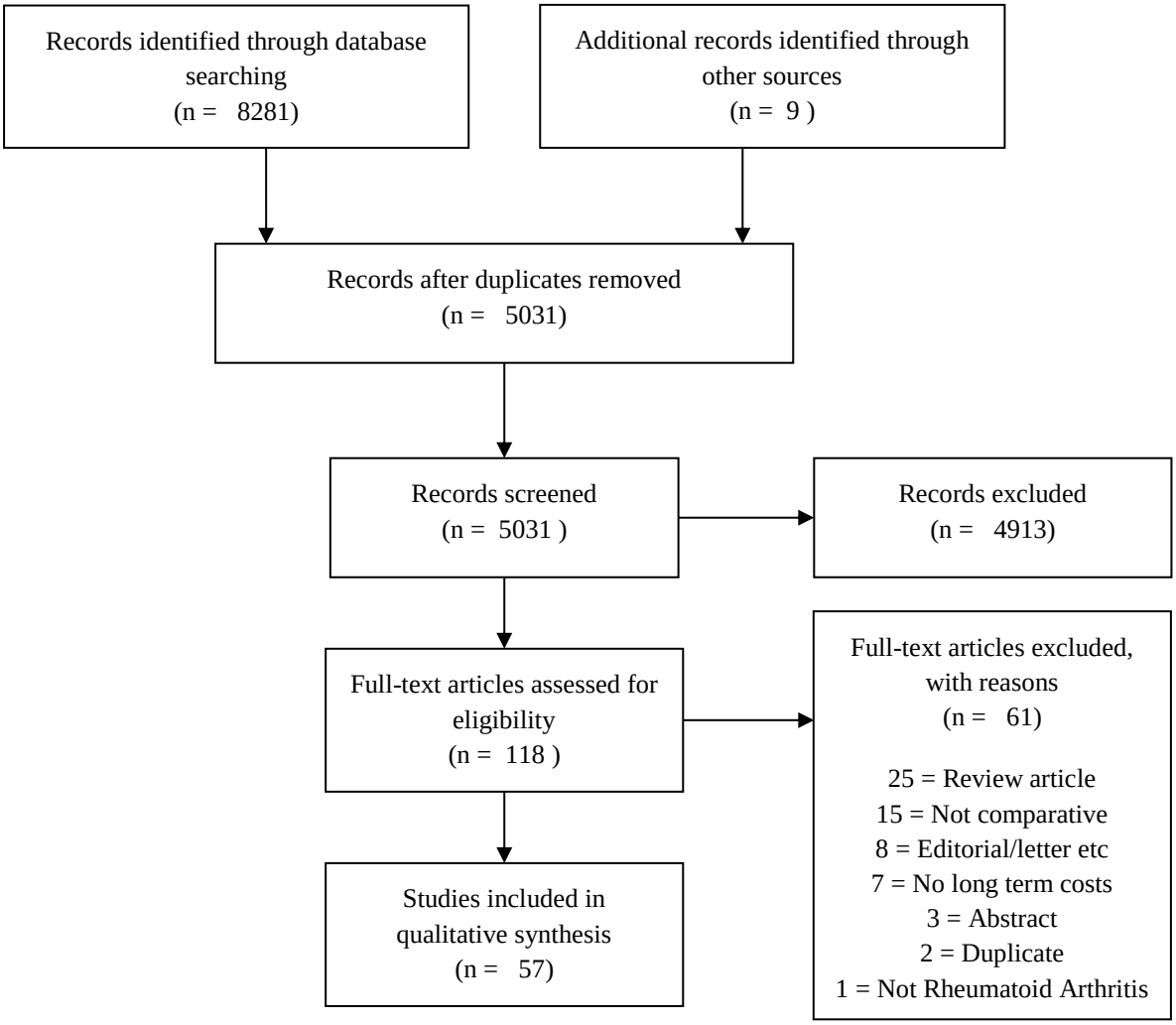

Table 1: Summary of recent-onset RA economic evaluations

Study , year	Country	Interventions	Time horizon	Type	Model type	Incremental Cost-effectiveness Ratio (ICER)
Chen et al. 2006[21]	UK	TNFα with or without MTX at first line or third line	Lifetime	CUA	ISM	ETA, ADA and INF after multiple cDMARD failure were £24k, £30k and £38k per QALY, respectively
Davies et al. 2009[22]	US	MTX vs. ADA+MTX vs. ETA vs. INF+MTX vs. ADA+MTX	Lifetime	CUA	ISM	INF and ETA extendedly dominated by ADA. ADA+MTX $47k per QALY vs. cDMARDs. ADA+MTX then ETA $42k per QALY vs. cDMARDs
Finckh et al. 2009[23]	US	Symptomatic therapy vs. MTX vs. bDMARDs	Lifetime	CUA	ISM	bDMARDs dominated by cDMARDs. cDMARDs ICER $4k per QALY vs. symptomatic therapy
Hartman et al. 2004[24]	Netherlands	Placebo vs. folic acid vs. folinic acid. Adjunct to MTX	48 weeks	CUA	TA	Placebo dominates folic acid. Folinic acid dominates placebo
Kavanaugh et al. 1996[37]*	US	GLD vs. MTX vs. bDMARDs	6 months	CCA	DT	Efficacy reflected as costs. GLD = $6k, MTX = $5k, bDMARDs = $9k
Kobelt et al. 2002[30]	UK	MTX vs. SSZ vs. LEF	10 year	CUA	MM	Using Strand et al, LEF dominates MTX. Using Emery et al, MTX dominates LEF. Using Smolen et al, LEF dominates SSZ.
Kobelt et al. 2011[25]	Sweden	ETA+MTX vs. MTX	10 year	CUA	MM	ETA+MTX ICER is €13k per QALY vs. MTX
Korthals-de Bos et al. 2004[31]	Netherlands	MTX+SSZ+Prednisolone vs. SSZ	56 weeks	CUA	n/a	Combo cDMARDs dominates SSZ

Maetzel et al. 2002[26]	Canada	Adding LEF to a cDMARD sequence	5 year	CUA	DT	Adding LEF ICER is Can$71k per QALY vs. cDMARD sequence
Schadlich et al. 2005[33]	Germany	Adding LEF to cDMARD sequences	3 years	CUA	DT	Adding LEF vs. cDMARD sequence is €8k per QALY
Schipper et al. 2011[27]	Netherlands	Sequential TNFα use	5 years	CUA	MM	TNFα €138k per QALY vs. MTX. ICER MTX+LEF €439k per QALY vs. MTX
Spalding et al. 2006[28]	US	MTX vs. bDMARD mono and combos	Lifetime	CUA	MM	$63k per QALY for ADA vs. MTX to $409k per QALY for INF vs. MTX.
Tosh et al. 2011[32]	UK	Alternative cDMARD mono and combo therapies	Lifetime	CUA	ISM	Monotherapy, Step-up, Parallel, Steroid are all dominated by step-down. Intensive £27k per QALY vs. step-down
van den Hout et al. 2009[34]	Netherlands	Comparing cDMARD combos vs. INF combo therapy	2 year	CUA	TA	Initial combination therapy with prednisone is likely to be the most cost-effective strategy at a WTP per QALY of <€100k
Verhoeven et al. 1998[29]	Netherlands	Step-down cDMARDs vs. SSZ	1 year	CUA	n/a	Combo cDMARDs dominates SSZ

*Unclear if recent-onset or established RA.

TNFα = Tumor necrosis factor-α (TNF-α) inhibitors, MTX = Methotrexate, ETA = Etanercept, ADA = Adalimumab, INF = Infliximab, cDMARD = conventional Disease Modifying Anti Rheumatic Drug, bDMARD = biologic Disease Modifying Anti Rheumatic Drug, LEF = Leflunomide, SSZ = Sulfasalazine. ICER = Incremental Cost Effectiveness Ratio, QALY = Quality Adjusted Life Year, CUA = Cost Utility Analysis, CCA, Cost Consequence Analysis, CEA = Cost-effectiveness Analysis, CMA = Cost Minimisation Analysis, WTP = Willingness to Pay, ISM = Individual Sampling Model, DT = Decision Tree, MM = Markov Model, TA = Trial Analysis, OA = Observational Analysis, CER = Cost Effectiveness Ratio, HCQ = Hydroxychloroquine, ANA = Anakinra, TOC = Tocilizumab, AM = Antimalarial, ABA = Abatacept, RTX = Rituximab, ILMM = Individual Level Markov Model, GLD = Gold

Table 2: Summary of established RA economic evaluations

Study , year	Country	Interventions	Time horizon	Type	Model type	Incremental Cost-effectiveness Ratio (ICER)
Anis et al. 1996[38]	Canada	CYA vs. AZA/PEN vs. placebo	1 year	CEA	DT	CYA ICER $11k per patient improved vs. placebo.
Bansback et al. 2005[39]	Sweden	TNFα with or without MTX vs. cDMARDs	Lifetime	CUA	ILMM	For all TNFα strategies, Using ACR50 response criteria €34k per QALY - €42k per QALY vs. cDMARDs. ADA+MTX likely to be the optimal
Barbieri et al. 2005[40]	UK	INF+MTX vs. MTX	1 year, lifetime	CUA	MM	INF-MTX ICER is £33k per QALY vs. MTX
Barton et al. 2004[41]	UK	ETA vs. INF vs. cDMARD sequence	Lifetime	CUA	ISM	ETA ICER £50k per QALY vs. basecase. INF ICER £68k per QALY vs. basecase. ETA ICER £28k per QALY vs. INF
Benucci et al. 2009[42]	Italy	ABA with LEF or MTX vs. ETA with LEF or MTX	2 year	CUA	OA	ETA+MTX had the lowest CER compared to baseline (non bDMARD tx) - €39k per QALY.
Benucci et al. 2011[43]	Italy	RTX vs. constant disease	6 month, 1 year	CUA	OA	RTX ICER €15k per QALY vs. consistent disease comparator (6 months). ICER €23k in 1 year
Beresniak et al. 2011[44]	Spain	ADA vs. INF vs. ABA vs. RTX	2 years	CEA	Unclear	Highest effectiveness and lowest CER for ABA. LDAS and RS outcomes
Brennan et al. 2004[46]	UK	ETA vs. cDMARD sequence	Lifetime	CUA	ISM	ETA ICER £16k per QALY vs. cDMARDs

Brennan et al. 2007[45]	UK	TNFα vs. cDMARDs	Lifetime	CUA	ISM	TNFα ICER is £23k per QALY vs. cDMARDs
Chiou et al. 2004[47]	US	ANA vs. ETA vs. ADA vs. INF	1 year	CUA	DT	ETA ICER $7k per QALY vs. ANA. ADA and INF dominated by ETA
Choi et al. 2000[48]	US	cDMARD mono and combo vs. bDMARD mono and combo	6 month	CEA	DT	ETA ICER $42k per ACR20 responder vs. triple cDMARD therapy.
Choi et al. 2002[49]	US	cDMARD mono / combo vs. bDMARD mono / combo	6 month	CEA	DT	ETA ICER $41k per ACR20 responder vs. MTX
Cimmino et al. 2011[50]	Italy	ABA vs. ADA vs. RTX vs. INF	2 year	CEA	Unclear	Highest effectiveness and lowest CER for ABA. LDAS and RS outcomes
Clark et al. 2004[51]	UK	Adding ANA in a treatment sequence	Lifetime	CUA	ISM	ANA ICER over £100k per QALY vs. standard care
Coyle et al. 2006[52]	Canada	GLD vs. bDMARD mono and combo	5 year	CUA	MM	INF and ETA had ICERS over $100k per QALY vs. cDMARDs
Diamantopoulos et al. 2012[53]	Italy	Sequential bDMARD use	lifetime	CUA	ISM	TOC dominates replacing ETA or ADA. TOC ICER €2k per QALY vs. INF. TOC ICER €17k when added first line.
Hallinen et al. 2010[54]	Finland	Sequential bDMARD use	Lifetime	CUA	ILMM	RTX dominates ADA, ABA, ETA after TNFα failure. RTX ICER €30k per QALY vs. BSC.

Jobanputra et al. 2002[55]	UK	Adding ETA and INF into a cDMARD sequence	Lifetime	CUA	ISM	ETA ICER £83k per QALY vs. basecase. INF ICER £115k per QALY vs. basecase. ETA ICER £44k per QALY vs. INF.
Kielhorn et al. 2008[56]	UK	RTX+MTX vs. cDMARD sequence	lifetime	CUA	ILMM	RTX ICER £11k per QALY vs. cDMARDs. With no sequential bDMARD us, RTX ICER £14 per QALY vs. cDMARDs.
Kievit et al. 2009[57]	Netherlands	Comparing treatment guidelines	6 month	CCA	TA	All strategies had an equal cost. All variations to guideline generated more responders.
Kobelt et al. 2003[59]	Sweden, UK	INF+MTX vs. MTX	10 year	CUA	MM	INF ICER is €3k per QALY vs. MTX in Sweden. £21k per QALY vs. MTX in UK
Kobelt et al. 2004[58]	Sweden	TNFα vs. cDMARDs	1 year	CUA	TA	TNFα ICER is €43k per QALY vs. previous years' therapy
Kobelt et al. 2005[60]	Sweden	ETA vs. MTX vs. ETA+MTX	2 year/ 10 year	CUA	MM	ETA+MTX ICER is €37k per QALY vs. MTX (2 year horizon). ETA+MTX ICER is €46k per QALY vs. MTX (109 year horizon)
Lekander et al. 2010[61]	Sweden	INF vs. cDMARDs	20 year	CUA	MM	INF ICER €22k per QALY vs. cDMARDs
Lindgren et al. 2009[62]	Sweden	RTX vs. TNFα	Lifetime	CUA	DES	RTX dominates TNFα

Maetzel et al. 2002a[63]	Canada	LEF vs. MTX vs. placebo	1 year	CCA	n/a	MTX dominates LEF and placebo
Malottki et al. 2011[64]	UK	ADA vs. ETA vs. INF vs. RTX vs. ABA vs. cDMARD	Lifetime	CUA	ISM	RTX dominates ADA, ETA and INF ABA ICER £130k per QALY vs. RTX
Marra et al. 2007[65]	Canada	INF+MTX vs. MTX	10 year	CUA	MM	INF ICER between $Can32k-70k per QALY vs. MTX.
Merkesdal et al. 2010[66]	Germany	Adding RTX+MTX to a sequence	Lifetime	CUA	ILMM	RTX ICER €24k per QALY vs. TNFα
Nuijten et al. 2001[67]	Netherlands	ETA vs. INF	1 year	CMA	Unclear	ETA dominates INF
Osiri et al. 2007[68]	Thailand	Comparing cDMARD strategies	1 year	CEA	n/a	MTX = $2k (per 1 point HAQ change vs. AM). MTX + AM = dominates. MTX + SSZ = $625. AM + SSZ = $14k. AM + MTX + SSZ = $1k. LEF = $1k. Other DMARDS = $16k
Rubio-Terrés et al. 2001[69]	Spain	INF+MTX vs. LEF	1 year	CMA	Unclear	LEF dominates INF+MTX in the CMA
Russell et al. 2009[70]	Canada	Sequential TNFα use	2 year	CEA	DT	1st bDMARD position: ABA dominates. 2nd bDMARD position: $20k per LDAS and $26k per remission vs. comparator sequence

Saraux et al. 2010[71]	France	Sequential TNFα use	2 year	CEA	Unclear	Lower costs per 'theoretical expected number of days in remission' with ABA after first TNFα compared with RTX.
Shini et al. 2010[72]	India	cDMARD mono and combo therapies	3 month	CEA	n/a	For mono, lowest CER was HCQ. For combo, lowest CER was MTX+HCQ
Soini et al. 2012[73]	Finland	ADA vs. ETA vs. TOC	Lifetime	CUA	ISM	TOC extendedly dominates ADA and ETA and €17k per QALY vs. MTX.
Tanno et al. 2006[74]	Japan	Adding ETA to a cDMARD sequence	Lifetime	CUA	MM	ETA ICER ¥3.5 per QALY vs. standard therapy
Vera-Llonch et al. 2008[75]	US	ABA vs. cDMARDs	Lifetime	CUA	ISM	ABA ICER $45k per QALY vs. cDMARDs
Vera-Llonch et al. 2008a[76]	US	ABA+MTX vs. MTX	Lifetime	CUA	MS	ABA+MTX ICER $43k per QALY vs. MTX
Wailoo et al. 2008[77]	US	ETA vs. ADA vs. ANA vs. INF	Lifetime	CUA	ISM	ANA was the least effective and least costly strategy. ETA, INF and ADA were similar in terms of effectiveness but INF was more costly.
Welsing et al. 2004[78]	Netherlands	Usual care vs. LEF vs. TNFα vs. LEF,TNFα sequences	5 year	CUA	MM	Post-DMARD failure most cost effective position for TNFα, with ICER of €163k per QALY vs. usual care.
Wong et al. 2002[79]	US	INF+MTX vs. MTX	Lifetime	CUA	MM	INF ICER is £30k per QALY vs. MTX

TNFα = Tumor necrosis factor-α (TNF-α) inhibitors, MTX = Methotrexate, ETA = Etanercept, ADA = Adalimumab, INF = Infliximab, cDMARD = conventional Disease Modifying Anti Rheumatic Drug, bDMARD = biologic Disease Modifying Anti Rheumatic Drug, LEF = Leflunomide, SSZ = Sulfasalazine. ICER = Incremental Cost Effectiveness Ratio, QALY = Quality Adjusted Life Year, CUA = Cost Utility Analysis, CCA, Cost Consequence Analysis, CEA = Cost-effectiveness Analysis, CMA = Cost Minimisation Analysis, WTP = Willingness to Pay, ISM = Individual Sampling Model, DT = Decision Tree, MM = Markov Model, TA = Trial Analysis, OA = Observational Analysis, CER = Cost Effectiveness Ratio, HCQ = Hydroxychloroquine, ANA = Anakinra, TOC = Tocilizumab, AM = Antimalarial, ABA = Abatacept, RTX = Rituximab, ILMM = Individual Level Markov Model, GLD = Gold

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