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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-rhuematic drugs only: systematic review and economic evaluation

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Matt Stevenson led the project and was involved in all aspects of the project. Rachel Archer led the systematic review along with Emma Simpson and Emma Everson-Hock, Jon Tosh constructed the mathematical model and undertook the review of economic evaluations. John Stevens undertook the network meta-analysis, Allan Wailoo liased with registry holders, provided advice and together with Monica Hernandez formulated statistical models based on these data. Suzy Paisley and Kath Williams formulated and ran the search strategies. David Scott and Adam Young provided clinical advice.

About ScHARR

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

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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

ABT	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
AKR	Anakinra
ALT	Autoregressive latent trajectory
AZA	Azathioprine
bDMARD	Biologic DMARD
BL	Baseline
BSRBR	British Society for Rheumatology Biologics Register
cDMARD	Conventional DMARD
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CRP	c-reacitve protein
CrI	Credible interval
CTZ	Certolizumab pegol
DAS	Disease Activity Score
DAS28	Disease Activity Score 28 joints
DMARD	Disease-modifying anti-rheumatic drugs
ETN	Etanercept
ERAS	Early Rheumatoid Arthritis Study
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAD	Final appraisal determination
GLD	Gold Injections
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health assessment questionnaire disability index
HCQ	Hydroxychloroquine
HR	Hazard ratio
i.a.	Intra-articular
i.m.	Intramuscular
i.v.	Intravenous
ICER	Incremental cost effectiveness ratio
IFX	Infliximab
JSN	Joint space narrowing
LEF	Leflunomide
Mon	monotherapy
MP	Methylprednisolone
MTC	Mixed treatment comparison
MTX	Methotrexate

NBT	Non-biologic therapy
NDB	National Data Bank for Rheumatic Diseases
NMA	Network meta-analysis
NOAR	Norfolk Arthritis Register
NA	Not applicable
NR	Not Reported
QALY	Quality adjusted life years
RA	Rheumatoid Arthritis
RTX	Rituximab
s.c.	Subcutaneous
SSZ	Sulfasalazine
TCZ	Tocilizumab
TNF	Tumour necrosis factor
TOF	Tofacitinib
VARA	Veterans Affairs Rheumatoid Arthritis
VAS	Visual analogue scale

2. EXECUTIVE SUMMARY

2.1 Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive, irreversible, joint damage, impaired joint function, pain and tenderness caused by swelling of the synovial lining of joints and is manifested with increasing disability and reduced quality of life. The primary symptoms are pain, morning stiffness, swelling, tenderness, loss of movement, fatigue and redness of the peripheral joints. RA is associated with substantial costs both direct (associated with drug acquisition and hospitalisation) and indirect due to reduced productivity.

In 2010 the ACR and EULAR jointly published a Rheumatoid Arthritis Classification Criteria, which focussed on features at earlier stages of disease that are associated with persistent and/or erosive disease rather than defining the disease by its late stage features. The classification criteria allocates scores to characteristics of: joint involvement; serology; acute-phase reactants; and duration of symptoms to produce a score between 0 and 10 inclusive, with those scoring 6 or greater and with obvious clinical synovitis being defined as having "definite RA" in the absence of an alternative diagnosis that better explains the synovitis.

There are an estimated 400,000 people in England and Wales with RA with approximately 10,000 incident cases per year. The disease is more prevalent in females (1.16%) than in males (0.44%) with the majority of cases being diagnosed when patients are between 40 and 80 years of age and with peak incidence in the 70s.

2.2 Objectives

The key objectives of this report are two-fold. These include estimating the clinical effectiveness of seven biologic disease modifying anti-rhuematic drugs (bDMARDs): adalimumab; etanercept; infliximab; certolizumab pegol; golimumab; tocilizumab; and abatacept in defined populations, and estimating the cost-effectiveness of these interventions compared with conventional disease modifying anti-rhuematic drugs (cDMARDs). These analyses incorporated the use of bDMARDs with and without methotrexate where this was within license.

Three populations were defined: Population 1, adults with severe active RA not previously treated with cDMARDs; Population 2, adults with severe active RA that have been previously treated with cDMARDs but not bDMARDs; and Population 3 adults with moderate to severe

active RA that have been previously treated with cDMARDs only, including methotrexate (unless contraindicated or inappropriate).

2.3 Methods

A systematic review of clinical effectiveness and safety evidence for interventions of interest was conducted. Separate network meta analyses (NMA) were undertaken for randomised controlled trials (RCTs) reporting EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology) data, with results presented dependent on whether RCTs with a small proportion of patients with prior bDMARD exposure or low prior MTX exposure were included.

A mathematical model was constructed to simulate the experiences of hypothetical patients. The model was based on EULAR response as this is most commonly used in clinical practice in England and Wales. Large observational databases, published literature and the results of the NMA were used to provide data for the model. The primary outcome measure was cost per QALY gained.

2.4 Results

Sixty randomised controlled trials met the inclusion criteria for the systematic review of clinical effectiveness and safety evidence. Of these, 37 trials provided relevant ACR and EULAR response data for the NMA. In addition, 14 additional trials not meeting review criteria contributed data to NMA sensitivity analyses. Other relevant efficacy and safety outcomes were tabulated and discussed in a narrative synthesis. Generally risk of bias was low overall, and low for baseline comparability, blinding, analysis by allocated treatment group and inclusion of ≥80% of participants randomised in the final analysis. There was greater risk of bias and a lack of clarity in many included trials for allocation sequence generation and concealment and selective reporting of outcomes.

Whilst there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in Population 1, infliximab + MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups; Intensive cDMARDs + prednisolone and adalimumab + MTX; etanercept, golimumab + MTX and step-up combination cDMARDs; adalimumab and cDMARDs.

Whilst there was uncertainty in, and overlap between the effects of treatment on EULAR for interventions in Population 2 and 3 in the main trials, etanercept + MTX and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: tocilizumab, golimumab + MTX, adalimumab + MTX, abatacept iv + MTX and grouped biologics; etanercept, infliximab + MTX, adalimumab and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly the same groupings, although certolizumab pegol + MTX was associated with an even bigger response than etanercept + MTX and tocilizumab + MTX.

Whilst there was uncertainty in, and overlap between the effects of treatment on ACR for interventions in Population 2 and 3 in the main trials, etanercept + MTX, tocilizumab and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups:,etanercept, golimumab + MTX, abatacept sc + MTX, adalimumab + MTX, infliximab + MTX and abatacept iv + MTX; certolizumab pegol + MTX, intensive cDMARDs and adalimumab. The inclusion of the additional studies in which patients received prior biologics suggested that certolizumab pegol + MTX and etanercept + MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and adalimumab which are associated with even smaller response rates.

The typical incremental cost per QALY of bDMARDs compared with a cDMARD alone strategy is typically over £50,000 per QALY when used in Populations 2 and 3. This is greater for those who receive a bDMARD without MTX. This is greater than £400,000 per QALY in Population 1. The key parameter which affected the results is the assumed Health Assessment Questionnaire whilst on cDMARDs; if the values used in previous National Institute for Health and Care Excellence (NICE) appraisals were instead used the incremental cost per QALY fell to below £35,000 in some scenarios for bDMARDs compared with cDMARDs alone. Fully incremental analyses were undertaken, but these could be misleading due to the similarity in incremental costs per QALY for each bDMARD compared with cDMARDs alone. The data source used for establishing the relationship between HAQ and pain was also seen to influence the results markedly; the Assessment Group basecase uses the estimate most favourable to the bDMARDS.

2.5 Discussion

There is no reason to believe that the results detailed in this report are not generalisable to the English and Welsh populations.

A strength of this report is that a systematic review of RCTs for bDMARDs in bDMARD-naïve patients has been conducted. The primary outcome measures are EULAR or ACR response at six-months and a formal NMA has been conducted to assess relative efficacy. Different analyses have been undertaken to assess the impact of including RCTs with a small proportion on patients with prior bDMARD use, and/or including RCTs when patients may have not had adequate prior MTX treatment.

A major strength of the cost-effectiveness analyses presented is that the Assessment Group has constructed a EULAR-based model that is much more appropriate to practice in England and Wales than previous ACR-based models. Estimates of ICERs for both EULAR data only, and when mapping ACR data to EULAR data indicate that the conclusions were not altered by restricting the selection of RCTs to only those that reported EULAR data.

An additional strength is that large observational databases were used to generate data on parameters such as HAQ change conditional on EULAR response and HAQ progression whilst on cDMARDs. This is preferable to data taken from relatively small RCTs of limited follow-up.

The model has known limitations. The plausible reduced efficacy of treatments when used subsequent to other treatments has not been formally incorporated. It is expected that this omissionwill favour bDMARDs. Additionally the effects of non-adherence to NICE guidelines (as shown in the British Society for Rheumatology Biologics Register) have not formally been incorporated; it is expected that were this included then the ICERs for bDMARDs compared with cDMARDs would increase and disfavour bDMARDs. Lost productivity has not been included in the model, which would favour bDMARDs if it were included.

The analyses have assumed that the discontinuation rule specified by NICE has been strictly adhered to; data from the BSRBR shows that this is not the case. If such non-adherence continues the ICERs will be considerably higher than those presented. Analysis of the impact has not been undertaken due to the possibility of back-calculation of commercial-in-confidence discounts offered through patient access schemes.

2.6 Conclusions

The implications for the National Health Service are not known ans it will be heavily dependent on the guidance produced by NICE. This could include reducing the expenditure on RA interventions, maintaining current levels or increasing the expenditure.

Key research priorities include establishing more precisely: HAQ progression whilst on cDMARDs; the relationship between HAQ score and utility; the relationship between HAQ score and pain. Better evidence on the relative efficacies of bDMARDs would be beneficial, but it is unlikely that this would occur given the large RCTs that would be required.

3. BACKGROUND

3.1. Description of health problem

Aetiology

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive, irreversible, joint damage, impaired joint function, pain and tenderness caused by swelling of the synovial lining of joints and is manifested with increasing disability and reduced quality of life.[1] The primary symptoms are pain, morning stiffness, swelling, tenderness, loss of movement, fatigue and redness of the peripheral joints.[2,3] RA is associated with substantial costs both direct (associated with drug acquisition and hospitalisation) and indirect due to reduced productivity.[4] RA has long been reported as being associated with increased mortality,[5,6] particularly due to cardiovascular events.[7]

Epidemiology

The initial classification criteria for RA were produced in 1987 by the American College of Rheumatology[8] (ACR). NICE Clinical Guideline 79 provides a summary of the ACR criteria namely that patients must have at least four of the seven criteria: morning stiffness lasting at least 1 hour; swelling in three or more joints; swelling in hand joints; symmetric joint swelling; erosions or decalcification on x-ray of hand; rheumatoid nodules; and abnormal serum rheumatoid factor. For the first four criteria these must have been present for at least a period of six weeks. However, in the clinical guideline the guideline development group preferred a clinical diagnosis of RA rather than the ACR criteria because ‘an early persistent synovitis where other pathologies have been ruled out needs to treated as if it is RA to try to prevent damage to joints. Identification of persistent synovitis and appropriate early management is more important than whether the disease satisfies classification criteria’ referencing the European League Against Rheumatism (EULAR) recommendations.[9]

In 2010 the ACR and EULAR jointly published a Rheumatoid Arthritis Classification Criteria, which focussed on features at earlier stages of disease that are associated with persistent and/or erosive disease rather than defining the disease by its late stage features.[10] The classification criteria allocates scores to characteristics of: joint involvement; serology; acute-phase reactants; and duration of symptoms to produce a score between 0 and 10 inclusive, with those scoring 6 or greater and with obvious clinical synovitis being defined as having “definite RA” in the absence of an alternative diagnosis that better explains the synovitis.

Two classifications have dominated the measurement of improvement in RA symptoms: ACR responses[11] and EULAR responses.[12]

The initial ACR response was denoted as an ACR20 which required: a 20% improvement in tender joint counts; a 20% improvement in swollen joint counts; and a 20% improvement in at least three of the following five 'core set items': Physician global assessment; Patient global assessment; patient pain; self-reported disability (using a validated instrument); and Erythrocyte sedimentation rate / C-reactive protein.

ACR response has been widely adopted in randomised controlled trials (RCTs) although[13] studies have shown that the value can vary between trials for an intervention due to the timing of the response. Since the inception of the ACR20 two other response criteria (ACR50 and ACR 70) have become more widely used, which are similar to ACR20 differing only in the level of improvements required to be denoted a responder.

In the UK monitoring the progression of RA is often undertaken using the disease activity score of 28 joints (DAS28). This assesses 28 joints in terms of swelling (SW28) and of tenderness to the touch (TEN28) and also incorporates measures of the erythrocyte sedimentation rate (ESR) and a subjective assessment (SA) on a scale of 0-100 made by the patient regarding disease activity in the previous week.

The equation for calculating DAS28 is as follows[14]

$$DAS28 = 0.56 * TEN28^{0.5} + 28 * SW28^{0.5} + 0.70 * \ln(ESR) + 0.014 * SA$$

The DAS28 can be used to classify both the disease activity of the patient and the level of improvement estimated within the patient.

The EULAR response criteria use the individual change in DAS28 and the level of DAS28 reached to classify trial participants as good, moderate or non-responders.[12] The EULAR response criteria and the ACR20 improvement criteria were found to have reasonable agreement in the same set of clinical trials[15], although Van Gestel et al state that the EULAR response criteria showed better construct and discriminant validity than did ACR20. EULAR response has been reported less frequently in RCTs than ACR responses, although EULAR is much more closely aligned to the treatment continuation rules stipulated by NICE that require a DAS28 improvement of more than 1.2 in order to continue treatment. The relationship

between change in DAS28 and the level of DAS28 reached with EULAR response is shown in Table 1. Dependent on the initial starting DAS score of the patient this would equate to either a good or moderate EULAR response, as shown in the second column of Table 1.

Table 1: Determining EULAR response based on DAS28[15]

	Improvement in DAS 28		
DAS28 at endpoint	>1.2	>0.6 and ≤1.2	≤0.6
≤ 3.2	good	moderate	non
>3.2 and ≤5.1	moderate	moderate	non
>5.1	moderate	non	non

The shaded cells indicate where patients continue treatment based on current NICE Technology Appraisals guidance

Patients with a DAS28 ≤3 .2 are stated as having inactive disease, those with a DAS28 > 3.2 and ≤5.1 are stated as having moderate disease and >5.1 as having very active disease.[14]

A widely used measure of patient disability is the health assessment questionnaire (HAQ). The HAQ is a patient completed disability assessment[16] which has established reliability and validity and has been used in many published randomised controlled trials in RA. HAQ Scores range from 0 to 3, with higher scores indicating greater disability and is a discrete scale with step values of 0.125, resulting in 25 points on the HAQ scale.

Incidence and prevalence

There are an estimated 400,000 people in England and Wales with RA,[17] with approximately 10,000 incident cases per year.[18] The disease is more prevalent in females (1.16%) than in males (0.44%)[18] with the majority of cases being diagnosed when patients are between 40 and 80 years of age[19] and with peak incidence in the 70s[18]. Traditionally, patients have been treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs) which include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF), and gold injections (GLD) as well as corticosteroids, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). However, more recently, a group of drugs have been developed consisting of monoclonal antibodies and soluble receptors that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes).[20] Such drugs have been labelled as biologic disease-modifying anti-rheumatic drugs (bDMARDs) and form the focus of this report.

Significance for the NHS

Due to previous NICE Technology Appraisals recommending a number of bDMARDs (see Section 3.2) with a potential sequence of three bDMARDs there has been a considerable increase in expenditure on RA interventions. Given the remit of this research to establish the clinical and cost-effectiveness of bDMARDs in advance of cDMARDs for patients with less severe disease (assumed to be those with a DAS28 score of between >3.2 and ≤5.1) there is potential for the expenditure to increase further should NICE guidance on these populations be positive. The majority of interventions are provided subcutaneously and would therefore require little additional staff time should there be positive guidance, although this would increase for those drugs which are given intravenously.

Further detailed information on the background of RA can be found within the relatively recent publication of the National Institute for Health and Care Excellence (NICE)'s Clinical Guidelines[20]. Additional information can also be located in the British Society for Rheumatology guidelines.[21]

3.2. Current service provision

Clinical Guidelines

For people with newly diagnosed RA, NICE Clinical Guideline 79[20] recommends a combination of cDMARDs (including MTX and at least one other DMARD plus short term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate (for example where there are comorbidities or pregnancy) DMARD monotherapy is recommended. Where DMARD monotherapy is used emphasis should be on increasing the dose quickly to obtain best disease control. For the purposes of this assessment the term intensive DMARDs has been used to denote that this is treatment with multiple cDMARDs simultaneously.

Current NICE Technology Appraisal Guidance

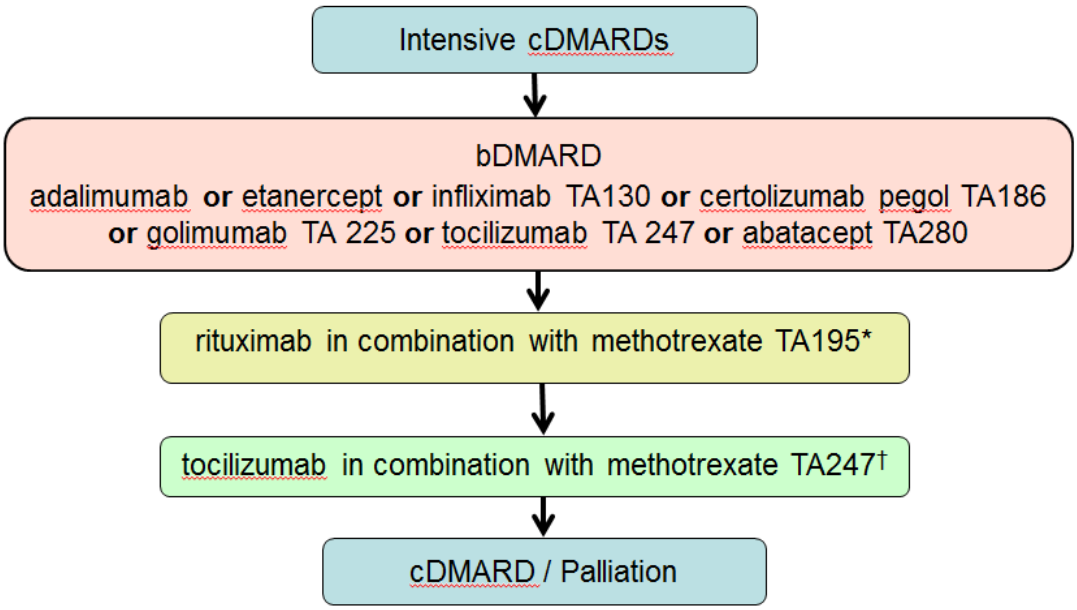
NICE guidance (Technology Appraisal (TA) 130, TA186 and TA225)[22-24] recommends the use of the tumour necrosis factor (TNF) inhibitors etanercept, infliximab, adalimumab, certolizumab pegol and golimumab in people with RA after the failure of two cDMARDs, including MTX, and who have a disease activity severity (DAS28) score greater than 5.1. Terminated NICE guidance (TA224) was unable to issue recommendations for the use of golimumab in people with rheumatoid arthritis that have not been treated with MTX.[25]

TA247[26] recommends tocilizumab as an alternative to TNF-inhibitors in the same circumstances as in TA130[27] that is in patients with a DAS28 score greater than 5.1, after a trial of two cDMARDs. NICE guidance TA280[28] recommends the use of intravenous abatacept in people with rheumatoid arthritis after the failure of cDMARDs in the same circumstances as TA130; the subcutaneous formulation has not been appraised.

A simplified summary of NICE recommend bDMARDs is shown in Figure 1. This defines the sequence of treatments that have received positive guidance for patients with a DAS28 score of >5.1. In summary, the typical route would be intensive cDMARDs followed by a bDMARD, followed by RTX plus MTX, then tocilizumab before returning to cDMARDs.

It is noted that NICE Clinical Guideline 79 recommends the use of intensive cDMARDs which have been assumed to be used rather than two cDMARDs used in monotherapy, although this latter option is acceptable.

Figure 1: Summary of the position of bDMARDs within NICE TA recommendations for sequence of treatments for patients with RA and a DAS28 score > 5.1



*If rituximab and MTX is contraindicated or withdrawn due to adverse events then the following can be used: adalimumab **or** etanercept **or** infliximab **or** abatacept in combination with MTX; adalimumab **or** etanercept monotherapy TA195 : tocilizumab in combination with MTX TA 247, assuming these have not been used previously in the sequence.

†Would no be used if tocilizumab has been used previously in the sequence

NICE has also issued guidance (TA195, TA225 and TA247[22,24,26]) on the treatment of rheumatoid arthritis after the failure of a TNF inhibitor but such guidance falls outside of the scope of the NICE appraisal.

NICE criteria for continuing treatment.

Each of the NICE technology appraisals states that in order for patients to continue treatment with a bDMARD that there must have been an improvement in DAS28 of at least 1.2 points at 6 months. If this criterion has not been met then treatment should be stopped and the next intervention in the sequence initiated.

Data were provided by the British Society for Rheumatology Biologics Register (BSRBR) to the Assessment Group (personal communication) and were used to assess the time on first biologic conditional on EULAR response. These indicate that over 25% of patients who had

no EULAR response at six months were still on treatment at 4.5 years, with the median treatment time being 319 days. This shows that there is not strict adherence to the NICE criteria for continuation of treatment. The majority of patients (94%) had a DAS28 score of >5.1 indicating that the severity criteria stated by NICE was reasonable well adhered to.

3.3. Description of the technologies under assessment

Interventions considered in the scope of this report.

The scope of the work is to ascertain the clinical and cost-effectiveness of seven interventions within three populations that will be detailed subsequently. These interventions are: abatacept; adalimumab; certolizumab pegol; etanercept; golimumab; infliximab; and tocilizumab. It is noted that abatacept can be delivered in two formulations: intravenously and subcutaneously and that both have been modelled separately. Due to the large number of interventions these have been initially summarised by mode of action. There then follows a summary of the UK marketing authorisation for each intervention along with a description of administration method. This text is similar to that within the protocol contained within Appendix 1. Whilst abbreviations have been defined for interventions and comparators these have been reserved for use in tables to preserve readability of the report.

Mode of action

Adalimumab, etanercept, infliximab, certolizumab pegol and golimumab all inhibit the activity of TNF-α, a pro-inflammatory mediator that is partly responsible for damage to the joints in RA.

Abatacept is a selective modulator of the T lymphocyte activation pathway. It binds to molecules on the surface of antigen presenting cells preventing full activation of the T lymphocytes and interrupting the inflammatory process.

Tocilizumab inhibits the activity of the cytokine interleukin-6 (IL 6), a pro-inflammatory that is also partly responsible for damage to the joints in RA.

Marketing licence and administration method.

Abatacept (Orencia, Bristol-Myers Squibb) in combination with MTX has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more cDMARDs including MTX or a TNF-alpha inhibitor. It can be administered by intravenous infusion or by subcutaneous injection.

Adalimumab (Humira, Abbott Laboratories), in combination with MTX, has a UK marketing authorisation for the treatment of moderate to severe, active RA in adults when the response to cDMARDs, including MTX, has been inadequate and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX. Adalimumab can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. It is administered subcutaneously.

Certolizumab pegol (Cimzia, UCB Pharma), in combination with MTX, has a UK marketing authorisation for the treatment of moderate to severe, active RA in adult patients when the response to cDMARDs, including MTX, has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. It is administered subcutaneously.

Etanercept (Enbrel, Pfizer), in combination with MTX, has a UK marketing authorisation for the treatment of moderate to severe, active RA in adults when the response to cDMARDs, including MTX (unless contraindicated), has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX. Etanercept can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. It is administered subcutaneously.

Golimumab (Simponi, Merck Sharp & Dohme), in combination with MTX, has a UK marketing authorisation for the treatment of moderate to severe, active RA in adult patients when the response to cDMARD therapy including MTX has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX. It is administered subcutaneously.

Infliximab (Remicade, Merck Sharp & Dohme), in combination with MTX, has a UK marketing authorisation for the reduction of signs and symptoms as well as the improvement in physical function in adults with active disease when the response to DMARDs, including MTX, has been inadequate. It is also licensed for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other cDMARDs. It is administered by intravenous infusion.

Tocilizumab (RoActemra, Roche), in combination with MTX, has a UK marketing authorisation for the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or

more DMARDs or tumour necrosis factor antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab is administered by intravenous infusion.

Current Usage in the NHS

There is widespread use of the interventions within the NHS. Robust values of the exact breakdown by intervention are not known.

Identification of important subgroups.

The current NICE guidance has already identified a subgroup by stating that to receive a bDMARD the patient must have received two cDMARDs and have active RA with a DAS28 score in excess of 5.1. The research questions within this report include: estimating the cost-effectiveness if the severity criteria were lessened to include patients with a DAS28 score greater than 3.2; and estimating the cost-effectiveness of using bDMARDs in advance of cDMARDs.

An important clinical subgroup encompasses those patients in whom bDMARDs cannot be given in combination with MTX. The clinical and cost-effectiveness of licenced bDMARDs in this population will be estimated in this assessment.

The anticipated costs associated with the interventions

The costs associated with each intervention needs to take into account a number of factors. These include: the acquisition cost of the drug (incorporating any patient access scheme (PAS)); the average weight of patients with RA for those interventions that are weight based; the administration costs associated with infusions and of district nurses performing subcutaneous injections; and any loading doses required in the first year.

The acquisition costs and dosing regimens were taken from the British National Formulary (www.bnf.org – accessed June 2013[29]) with details of PASs taken from the manufacturers' submissions.

The average weights of patients with RA were estimated using data (n = 12,176) from the BSRBR [Personal Communication]. To be able to be used with all of the weight-based dosing regimens a large number of categories were required as detailed in Table 2. From these categories the average cost per dose for those with a weight-based dose can be calculated.

Table 2: The weight distribution of patients with RA using BSRBR data

Weight category (kg)	Number of Patients	Proportion of total patients
0-30	3	0.0%
31-33	7	0.1%
34-35	9	0.1%
36-45	240	2.0%
46-50	484	4.0%
51-60	2333	19.2%
61-67	2115	17.4%
68-70	949	7.8%
71-75	1310	10.8%
76-85	2148	17.6%
86-95	1351	11.1%
96-100	412	3.4%
101-133	734	6.0%
134-167	67	0.6%
168-200	14	0.1%
	12,176	100%

Additional loading doses in the first year were calculated based on the relevant regimen and the administration cost. Table 3 provides a simplified summary of the assumed mean acquisition costs per intervention and should be used to provide indicative rather than exact values. This is due to the fact that within the mathematical model described later, timings of costs are explicitly incorporated and also that in some subgroups the distribution of weights may differ from that of the full BSRBR database, a factor also considered within the Assessment Group model.

Additional treatments in a sequenced strategy.

Due to the nature of RA treatment being sequenced it was necessary for the Assessment Group and the manufacturers to incorporate the costs and effectiveness of rituximab into the model as this has positive NICE guidance following the withdrawal of a bDMARD. These will be discussed as applicable.

Table 3: The assumed mean acquisition costs for each intervention

Treatment	Dose regimen	Details of PAS if applicable	Cost per cheapest available dose (dose)	Cost per weight-adjusted dose [1] / standard regimen	Administration costs per treatment	Cost per Year (excluding admin costs) [2]	Additional Costs in Year 1
Abatacept (intravenous)	500 mg below 60 kg, 750 mg between 60-100 kg, 1000 mg above 100 kg; 0, 2 and 4 weeks then every 4 weeks thereafter	[redacted]	[redacted] (250mg)	[redacted]	£154	[redacted]	[redacted]
Abatacept (subcutaneous)	125mg weekly following loading dose 500 mg below 60 kg, 750 mg between 60-100 kg, 1000 mg above 100 kg.	[redacted]	[redacted] (125mg)	[redacted]	£3.05	[redacted]	[redacted]
Adalimumab	40 mg; every other week	N/A	£352.14 (40mg)	£352.14	£3.05	£9223.50	£-
Certolizumab pegol	400 mg per week initially, repeated at weeks 2and 4 weeks followed by a maintenance dose of 200 mg every 2 weeks	Initial 10 doses free	£357.50 (200 mg)	£357.50	£3.05	£9830.86	-£2628.50 [3]
Etanercept	50 mg; every week	N/A	£178.75 (50mg)	£178.75	£3.05	£9430.86	£-
Golimumab	50 mg below 100 kg, 100 mg above 100 kg, per month	100mg dose provided at the same price as the 50mg dose	£762.97 (50mg)	£762.97 [4]	£3.05	£9430.72	£-
Infliximab [5]	3 mg/kg: 0, 2, 6 then every 8 weeks	N/A	£419.62 (100mg)	£1110.98	£154	£8222.40 [6]	£1820.47
Tocilizumab	8 mg/kg every four weeks	[redacted]	[redacted] (80mg)	[redacted]	£154	[redacted]	£-

[1]Assuming the weight distribution of patients from the BSRBR and choosing the least expensive method of meeting the requirement. The correct dose for a specific patient is calculated within the model. [2]Assuming no vial sharing [3]This value has been simplified for clarity and is negative due to assuming 10 free doses in year 1 as detailed in the patient access scheme. The model calculates the timing and number of doses correctly. [4]Assuming that the cost of 100mg syringes are set to the price of 50mg syringes as per the previously agreed patient access scheme. [5]These values have been simplified for clarity, assuming 8 doses in year 1 and 6.5 in each subsequent year. The model calculates the timing and number of doses correctly. [6]Assuming no increase in dose requiring additional vials, - if the response is inadequate after 12 weeks, the dose may be increased in steps of 1.5 mg/kg every 8 weeks, up to max. 7.5 mg/kg every 8 weeks; alternatively, 3 mg/kg may be given every 4 weeks.
N/A – not applicable

4. DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

The aim of this assessment was to investigate the clinical and cost-effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of RA not previously treated with bDMARDS compared with each other and compared with cDMARDs.

Interventions

A detailed description of each of the interventions is provided in section 3.3. Table 4 summarises the relationship between the market authorisation and the decision problem detailed in section 4.2 i.e. whether the intervention is licensed to be used: prior to the initiation of methotrexate intervention; as a monotherapy (i.e. without needing to be given in combination with MTX); for patients with severe RA; and for patients with moderate to severe RA.

Table 4: The relationship between the licence of the intervention and the decision problem

	Is the intervention licensed……			
Intervention	prior to the use of MTX?	as a monotherapy?	for patients with severe RA?	for patients with moderate to severe RA?
Abatacept [a]			✔	✔
Adalimumab	✔	✔	✔	✔
Certolizumab pegol		✔	✔	✔
Etanercept	✔	✔	✔	✔
Golimumab	✔		✔	✔
Inflixumab	✔		✔	✔
Tocilizumab		✔	✔	✔

[a] Intravenous and subcutaneous formulations of abatacept have been combined as the market authorisations are identical.

Populations (including subgroups).

The scope issued by NICE defines three distinct populations with RA and includes (1) adults with severe active RA not previously treated with cDMARDs, (2) adults with severe active RA that have been previously treated with cDMARDs but not bDMARDs and (3) adults with moderate to severe

active RA that have been previously treated with cDMARDs only, including methotrexate (unless contraindicated or inappropriate). Henceforth, these will be referred to as Population 1, Population 2 and Population 3.

Although the NICE scope did not specify the definition of severe active RA and moderate to severe active RA, the following definition (based on expert clinical advice to the Assessment Group) has been adopted: 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.

As the scope issued by NICE explicitly defined subgroups, no further subgroups will be assessed, with the exception of those patients in which bDMARD treatment needs to be given as monotherapy. Separate analyses will be conducted for those in whom MTX can be tolerated and in those who can only receive bDMARD monotherapy.

The Assessment Group has chosen to deviate from the scope for Population 1 as the definition in the scope stated that MTX needed to have been used previously. Given this definition the populations were mutually exclusive but not exhaustive, as patients without prior bDMARD treatment who had not received MTX but had instead received an alternative cDMARD would not be allocated to any of the populations. In consultation with NICE and our clinical experts the Assessment Group broadened their interpretation of Population 1 to allow previous treatment with any cDMARD.

It is noted that the number of interventions considered in Population 1 is fewer than for Population 2 or 3, since only four interventions (adalimumab; etanercept; golimumab; and infliximab) are licensed in this population

Populations outside of the scope of the research

The following groups were explicitly excluded from the research by the scope issued by NICE.

- The initiation of treatment in patients without active RA
- Patients with a DAS score below 3.2 where they have received previous treatment with cDMARDs
- Patients with a DAS score below 5.1 if they have not been previously treated with cDMARDs
- Patients who have been previously treated with one or more bDMARDs.

Relevant comparators

The relevant comparators within the final scope differ according to the population considered. The scope stated that tofacitinib would be included if NICE had issued positive guidance prior to the report's completion, but this did not occur and therefore tofacitinib was not evaluated.

i) For severe active rheumatoid arthritis not previously treated with MTX or other DMARDs:

- Combination therapy with cDMARDs (including MTX and at least one other DMARD, such as sulfasalazine and leflunomide as recommended in NICE CG79)
- The interventions will be compared with each other

ii) For severe active rheumatoid arthritis that has been previously treated with cDMARDs only:

- Management strategies involving further cDMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
- The interventions will be compared with each other

iii) For moderate to severe active arthritis that has been previously treated with cDMARDs only:

- Management strategies involving further cDMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
- The interventions will be compared with each other

Outcomes

The outcome measures to be considered include:

- Disease activity
- Physical function
- Joint damage
- Pain
- Mortality
- Fatigue
- Radiological progression
- Extra-articular manifestations of disease
- Adverse effects of treatment
- Health-related quality of life

Data were also collected on a number of variables such as disease duration, number of previous cDMARDs, percentage of patients who had received bDMARDs in case there was sufficient variation

in baseline measurements that these could be investigated as treatment effect modifiers within data synthesis.

4.2 Overall aims and objectives of assessment

The review aims to:

- evaluate the clinical effectiveness of each intervention in affecting key outcomes in patients within each of the defined subgroups
- evaluate the adverse effect profile of each intervention (and comparator)
- estimate the incremental cost effectiveness within each of the defined subgroups of each intervention compared with all comparators
- estimate the possible overall cost of amending the current provision of interventions in the light of the cost-effectiveness results produced.
- identify key areas for primary research

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review of the literature and network meta-analyses (NMA) were conducted in order to evaluate the clinical effectiveness of abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab in the first line bDMARD treatment of adults with RA.

The systematic review of the evidence was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).

5.1 Methods for reviewing effectiveness

5.1.1 Identification of studies

The aims of the search were to provide as comprehensive retrieval as possible of clinical effectiveness evidence relating to abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab and to identify additional relevant treatments for potential inclusion in the NMA.

a) Electronic databases

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

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1948 to July 2013
- EMBASE (Ovid) 1980 to July 2013
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996 to May 2013
- Cochrane Central Register of Controlled Trials (Wiley Interscience) 1898 to May 2013
- Health Technology Assessment Database (Wiley Interscience) 1995 to May 2013
- Database of Abstracts of Review of Effects (Wiley Interscience) 1995 to May 2013
- Cumulative Index to Nursing and Allied Health Literature (EBSCO) 1982 to April 2013
- Toxline to July 2013

Given the broad scope of interventions to be included in the review and the high volume of potentially relevant studies to be sifted, the keyword searches of electronic resources were undertaken in three stages. No language or date restrictions were applied to any database. Details of keywords strategies are reported in Appendix 2.

Stage 1 was undertaken using keywords relating to the population only (i.e. RA) and did not include keywords relating to the interventions specified in the decision problem. The purpose was to keep the scope of the search broad in order to identify potentially relevant evidence for inclusion in the NMA, in addition to identifying RCTs and systematic reviews of the interventions of interest. For the searches of Medline, EMBASE, and CINAHL, methodological filters were added to restrict search results to RCTs and systematic reviews. In order to maximise the efficiency of the search process at this stage, filters aimed at maximising the precision of search results were applied.[30-34]

Stage 2 was undertaken using keywords relating to the population (RA) combined with keywords relating to the interventions of interest (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab) and any interventions identified as potentially allowing indirect comparisons to be made within the NMA. Keyword synonyms relating to the interventions included generic drug names, product names and drug registry numbers. The purpose of Stage 2 was to identify RCTs that might not have been retrieved by the 'high precision' Stage 1 searches. Therefore, RCT search filters aimed at maximising the sensitivity of search results were applied.[32,35] In the first instance, Medline and EMBASE were searched. Given the high volume of references retrieved, and the low yield in terms of relevant references identified it was decided that searches would not be extended to other databases or to other treatments to be potentially included in the NMA.

Stage 3 involved the undertaking of searches for potential supplementary adverse events evidence through the combination of keywords relating to the population (RA) with keywords relating to the interventions of interest (abatacept, adalimumab, atacicept, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, tofactinib). For the searches of Medline and EMBASE, adverse events filters were applied,[36] whereas no filter was required for the Toxline database.

Where possible, and in order to minimise duplication between search results, the results retrieved by earlier search strategies were excluded from the results retrieved by later search strategies using the 'not' boolean operator. The results retrieved by the Medline and EMBASE high precision searches (Stage 1) were excluded from Medline and EMBASE high sensitivity searches (Stage 2). The results retrieved by the Medline and EMBASE high precision and high sensitivity searches (Stage 1 and 2) were excluded from the adverse events searches (Stage 3).

b) Other resources

To identify additional studies, the reference lists of relevant studies (including existing systematic reviews) were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify

articles that cite the relevant articles. It was originally intended in the protocol (Appendix 1) that searches be performed to identify ongoing research and unpublished studies using the Current Controlled Trials *meta*Register of Controlled Trials (mRCT), the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP), the European Union Clinical Trials Register (EU-CTR), the Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites and the WOS Conference Proceedings Citation Index – Science (CPCI-S). However, this was not possible within the timescales dictated by the NICE appraisal process. Handsearching of relevant documents included sponsor submissions to the NICE technology appraisal update process, recent systematic reviews, and documentation associated with previous relevant NICE technology appraisal guidance (TAs 130, 186, 224, 234, 225, 247). Grey literature was also sought using the sources listed in the international grey literature search toolkit produced by the Canadian Agency for Drugs and Technologies in Health (CADTH).[37]

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

5.1.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria for the selection of clinical effectiveness and safety evidence were defined according to the decision problem outlined in the NICE scope.[38]

The inclusion of potentially relevant articles was undertaken using a two-step process. Firstly, all titles and abstracts were examined for inclusion by one reviewer. Any citations that clearly did not meet the inclusion criteria (e.g. animal studies, studies unrelated to RA) were excluded. Secondly, full text articles were initially examined by one reviewer. It was intended in the original protocol that a second reviewer would check approximately 10% of citations. However, due to the very large number of citations identified in the clinical effectiveness searches, this was not possible in the timescales available for this appraisal process. Any uncertainty in the inclusion and exclusion of potential full text articles was resolved through discussion with the review team. Where agreement could not be reached, expert clinical advice was sought for a final decision.

The relevance of each article for the systematic review was assessed according to the following criteria:

a) Population

As detailed in Section 4, the three populations under consideration in this assessment were:

i) Adults with severe active RA not previously treated with methotrexate (defined by a DAS score of ≥ 5.1). In the original protocol (Appendix 1) this population was defined as "adults with severe active RA not previously treated with methotrexate or other DMARDs (defined by a DAS score of ≥ 5.1)." However, this definition was subsequently modified and broadened by the Assessment Group (in consultation with clinical experts) to include "adults with severe active RA not previously treated with methotrexate" in order to permit the inclusion of trial populations relevant to the decision problem which were methotrexate-naïve but may have had some prior experience of other cDMARDs.

ii) Adults with severe active RA that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate) (defined by a DAS score of ≥ 5.1).

iii) Adults with moderate to severe active RA that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate) (defined as a DAS score between 3.2 and 5.1).

The following populations were considered outside the appraisal scope and were therefore excluded:

- Patients with a DAS score below 3.2
- Patients with a DAS score below 5.2 if they have not been previously treated with methotrexate
- Patients who have been previously treated with one or more biologic DMARDs

b) Interventions

The following interventions were included:

i) For RA not previously treated with methotrexate:

- Adalimumab
- Etanercept
- Infliximab
- Golimumab

ii) For RA that has been previously treated with conventional DMARDs only:

- Adalimumab
- Etanercept
- Infliximab
- Certolizumab pegol
- Golimumab
- Abatacept (intravenous and subcutaneous preparations)

- Tocilizumab

The above interventions were assessed in accordance with licensed indications and could be delivered in conjunction with cDMARDs or as monotherapy (as defined in licensed indications).

c) Comparators

The relevant comparators differed according to the population considered and included the following:

i) For severe active RA not previously treated with methotrexate:

- Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) or DMARD monotherapy with dose escalation
- Biologic interventions vs. each other

ii) For severe active RA that has been previously treated with conventional DMARDs only:

- Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
- Biologic interventions vs. each other

iii) For moderate to severe active RA that has been previously treated with conventional DMARDs only:

- Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
- Biologic interventions vs. each other

d) Outcomes

The outcome measures under consideration included:

- Disease activity (including DAS28, ACR and EULAR responses, swollen and tender joint counts and patient and physician global assessments of disease activity)
- Physical function (including HAQ-DI)
- Joint damage / radiological progression
- Pain
- Mortality
- Fatigue
- Extra-articular manifestations of disease
- Health-related quality of life
- Adverse effects of treatment

e) Study design

The systematic review of clinical effectiveness was based on RCT evidence. It was stated in the protocol (Appendix 1) that, if insufficient data were available from RCTs, observational studies or non-randomised trials may be considered, for example for safety evidence. The Assessment Group supplemented the adverse events data identified in the included RCTs with safety data from long-term extension studies reporting on individual included RCTs. Studies published as abstracts or conference presentations were only included if sufficient details were presented to allow both an appraisal of the methodology and an assessment of the results to be undertaken. Systematic reviews could be used as potential sources of additional references of efficacy evidence.

The following study types were also excluded:

- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Studies presenting secondary analyses of RCT data or pooled RCT data
- Non-English language papers

5.1.3 Data abstraction and critical appraisal strategy

Data relevant to the decision problem were extracted by one reviewer. Data were extracted without blinding to authors or journal. Study arms where intervention treatments were administered in line with licensed indications were extracted; where there was a slight divergence between the regimen used in the RCT and the licensed regimen this was explicitly highlighted. It was proposed in the original protocol (Appendix 1) that at least 10% of data extraction forms be checked by a reviewer. However, the Assessment Group ensured that all data included in the NMA were double checked by a second reviewer. For data not contributing to the NMA, data were extracted for the following time points: primary endpoint (for selected efficacy data), latest available controlled RCT endpoint (for efficacy and safety data) and latest available long-term extension study endpoint (for safety data only). The safety data extracted were informed by the Summary of Product Characteristics (available at http://www.medicines.org.uk/emc/) and FDA prescribing information for each intervention[39-45] Graphical data contributing to the NMA were estimated using Engauge software (version 4.1) (2011)[46] and graphical data not contributing to the NMA were estimated manually by a reviewer. Where multiple publications of the same study were identified, data extraction was undertaken on all relevant associated publications, and findings were presented as a single study. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

The methodological quality of each included study was assessed by one reviewer. It was originally intended in the protocol (Appendix 1) that quality assessment would be checked by a second reviewer, but this was not feasible within the timescales available for the appraisal process. The quality assessment of included studies was informed by selected items listed in the NHS CRD report[47] and Cochrane Risk of Bias tool.[48] Additional quality issues specific to the assessment of rheumatoid arthritis RCTs (as described by Karsh *et al*., 2011) were also considered during the evaluation of studies.[49]

5.1.4 Methods of data synthesis

The extracted data and quality assessment variables were presented for each study, both in structured tables and as a narrative description.

As the identified evidence base permitted the undertaking of network meta-analyses for the estimation of treatment effects, supplementary meta-analyses were not undertaken. Network meta-analyses were conducted to determine efficacy using two different disease activity measures (ACR and EULAR responses).

5.1.5 Methods for the estimation of efficacy using network meta-analysis

5.1.5.1 Selection of evidence contributing to the network meta-analysis

Evidence considered relevant to the decision problem was selected according to the additional inclusion criteria detailed below.

- RCTs presenting ACR response or EULAR response data at any assessment time point between 22 and 30 weeks. The selection of this time frame and assumption that treatment effects would be broadly comparable across these assessment points was made in conjunction with the clinical advisors to the assessment. This criterion is broadly in line with previous data syntheses summarised by Thorlund *et al.* (2013)[50]; nine of the 13 mixed treatment comparison meta-analyses of biologic interventions for rheumatoid arthritis also employed an assessment time point in the region of 24 weeks / 6 months, in the remaining four MTCs three used 12 week data whilst one used between 50 and 55 weeks.[50]
- 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
- RCTs were not excluded from the base case on the basis of geographical location (a decision made in consultation with clinical advisors)
- RCTs were permitted in the base case where it was not indicated whether bDMARDs had been given (and no proportion of bDMARD use was provided), even if trial eligibility did not exclude prior bDMARDs

- Trials reporting a small proportion of patients with prior bDMARD experience (≤ 20%) were not included in the base case analyses but were explored via sensitivity analyses

Sensitivity analyses were also undertaken to include trials relevant to populations 2 and 3 where the population may not have adequately failed cDMARDs (either there was a sufficient response, MTX treatment duration was too short or a proportion of the population were MTX-naive).

Evidence was sought in which bDMARDs not considered as interventions or comparators within the NICE scope were evaluated in head to head trials with an included intervention in the first line treatment of RA. In order to establish whether any such identified data could be used to inform indirect comparisons within the NMA, a review of these interventions against cDMARDs was undertaken. If such trials were found and met the inclusion criteria for the review, then the bDMARD was considered part of the evidence base for the NMA.

A number of assumptions relating to the evidence base were made in conjunction with clinical advisors: i) It was assumed that all cDMARDs had the same efficacy; ii) It was also assumed that having failed a cDMARD was equivalent to having failed MTX; iii) Trials that included the use of immunosuppressants or single intra-articular glucocorticoid were also permitted, assuming that this would not change the efficacy of cDMARDs; iv) It was assumed that DAS28-CRP and DAS28-ESR are interchangeable where only one is reported. If both were reported, DAS28-ESR was used as this was reported most regularly (a decision made in consultation with clinical advisors).

5.1.5.2 Statistical model for the network meta-analysis

EULAR and ACR outcomes are ordered categorical data. EULAR has three categories (No response, Moderate response and Good response) and ACR has four categories (No response, ACR20, ACR50 and ACR70). ACRXX represents an improvement of at least XX%; in the analysis, the categories are treated as mutually exclusive so that patients cannot be in more than one category.

The model for the data assumes that the treatment effect is the same irrespective of the category. The likelihood function for the data is described as follows:

- Let r_{ikj}represent the number of patients in arm k of trial i in the mutually exclusive category $j = 1,2, \dots J$

The responses r_{ikj} will follow a multinomial distribution such that

$$r_{ikj=1,\ldots,J} \sim \text{Multinomial}(p_{ikj=1,\ldots,J}, n_{ik}),\ \sum_{j=1}^{J} p_{ikj=1,\ldots,J} = 1$$

The parameters in the model are the probabilities, p_{ikj}, that a patient in arm k of trial i has a response equivalent to category j.

We use a probit link function to map the probabilities, p_{ikj}, onto the real line such that:

$$\theta_{ikj} = \Phi^{-1}(p_{ikj}) = \mu_{ij} + \delta_{i,bk} I_{k\neq 1}$$

so that

$$p_{ikj} = \Phi(\mu_{ij} + \delta_{i,bk} I_{k\neq 1}).$$

In this model, the effect of treatment is to change the probit score of the control arm by $\delta_{i,bk}$ standard deviations.

The study-specific treatment effects, $\delta_{i,bk} I_{k\neq 1}$, are assume to arise from a common population distribution with mean treatment effect relative to the reference treatment, which in this analysis is cDMADs, such that:

$$\delta_{i,1k} \sim N(d_{t_{i1},t_{ik}}, \tau^2)$$

We further assume that there is an underlying continuous latent variable which has been categorised by specifying cut-offs, z_{ij}, which correspond to the point at which an individual moves from one category to the next in trial i. The model is re-written as:

$$p_{ikj} = \Phi(\mu_i + z_{ij} + \delta_{i,bk} I_{k\neq 1}).$$

The z_{ij} can be treated as fixed, which would assume that these points are the same in each trial and each treatment. Alternatively, they can be treated as random in which they are assumed to vary according to the trial but that within a trial they are the same such that:

$$z_{ic} \sim N(\nu_c, \sigma_z^2).$$

We used a model in which the z_{ij} were treated as being random because this resulted in a much better fit of the model to the data.

In some trials, the reported categories are a subset of the full set of categories so that there is overlap between categories. The multinomial likelihood is re-written as a series of conditional Binomial distributions such that for trial i reporting the number of patients, r_{ikj}, in category $j = 1, \dots, J-1$, we write:

$$r_{ikj} \sim \text{Binomial}\left(q_{ikj}, N_{ikj}\right), j = 1, \dots, J-1$$

where

$q_{ik1} =$ Prob(Outcome in category 1 of trial i)
$q_{ik2} =$ Prob(Outcome in category 2 of trial i | not in category 1)
…
$q_{ikj} =$ Prob(Outcome in category j of trial i | not in categories 1,2,…,$j-1$)
and
$N_{ikj} = n_{ik} - \sum_{u=1}^{j-1} r_{iku}$.

Further details of the model are presented in Dias et al.[51]

All analyses were conducted in the freely available software package WinBUGS.[52]

The model is completed by giving the parameters prior distributions.

When there is sufficient sample data, we can use conventional reference prior distributions and these will have little influence on the posterior results. The reference prior distributions used in the analyses were:

- Trial-specific baselines, $\mu_i \sim N(0, 1000)$
- Treatment effects relative to reference treatment, $d_{1t} \sim N(0, 1000)$
- Between study standard deviation of treatment effects, $\tau \sim U(0,2)$
- Population cut-offs, $\upsilon_{c_j} = \upsilon_{c_{j-1}} + \upsilon_{c'}$, $\upsilon_{c'} \sim U(0,5)$
- Between study standard deviation of cut-offs, $\sigma_z^2 \sim U(0,2)$

In the case of the analysis of the EULAR data there were relatively few studies and too few to update the between study standard deviation. Without Bayesian updating, a reference prior distribution that does not represent genuine prior belief will have a significant impact on the results and give posterior distributions that are unlikely to represent genuine posterior beliefs. To allow for this, we used a weakly informative prior distribution for the between study standard deviation such that $\tau \sim HN(0, 0.32^2)$.

To estimate the absolute probabilities of being in each category for each treatment, we used a Binomial likelihood function for the number of patients, r_{ik1} in each study that were classified as "No response" when treated with cDMARDs such that:

$$r_{ik1} \sim \text{Binomial}(n_{ik}, p_{ik1}).$$

We used a probit link function such that:

$$\Phi^{-1}(p_{ik1}) = \mu_i^{'}.$$

We assume that the study-specific baselines arise from population of effects such that:

$$\mu_i^{'} \sim N(\mu_b, \tau_b^2).$$

The model was completed by giving the parameters prior distributions such that:

- $\mu_b \sim N(0, 1000)$
- $\tau_b \sim U(0, 2)$

Again, there were relatively few studies providing data on the EULAR outcome so a weakly informative prior distribution was used for the between study standard deviation such that: $\tau \sim HN(0, 0.32^2)$.

For the baseline and network meta-analyses, we used a standard burn-in of 100,000 iterations of the Markov chain and retained 25,000 iterations to estimate parameters. In addition, the network meta-analyses exhibited moderately high correlation between successive iterations of the Markov chains so the chains were thinned by retaining every 10th sample.

For EULAR and ACR, analyses were performed according to whether the patient was MTX-experienced or whether patients were MTX-naïve. In addition, for patients who were MTX-experienced, EULAR was analysed according to the main trials and trials that included patients who received prior biologics (with and without the AMBITION study) and ACR was analysed according to the main trials, trials that included patients who received prior biologics (with and without AMBITION) and trials that included patients who were MTX naive.

We also explored the possibility that duration of disease was a treatment effect modifier. This was done for the main studies that provided ACR data. We did not attempt to adjust EULAR data for duration of disease because of the limited number of studies available. Duration of disease was centred in the model by subtracting the mean duration of disease across studies. Various models could be explored including having a separate treatment effect modifier for each treatment or allowing the treatment effect modifiers to be exchangeable across treatments. Again, because of the limited number of studies available we restricted attention to an exchangeable treatment effect modifier model. The model was completed by giving the common slope a N(0, 1000) prior distribution and the between slope standard deviation a U(0, 10) prior distribution. Results are not presented adjusted for duration of disease because the evidence suggested that it was not a treatment effect modifier (DIC Adjusted=1027.94, DIC Unadjusted 1026.74).

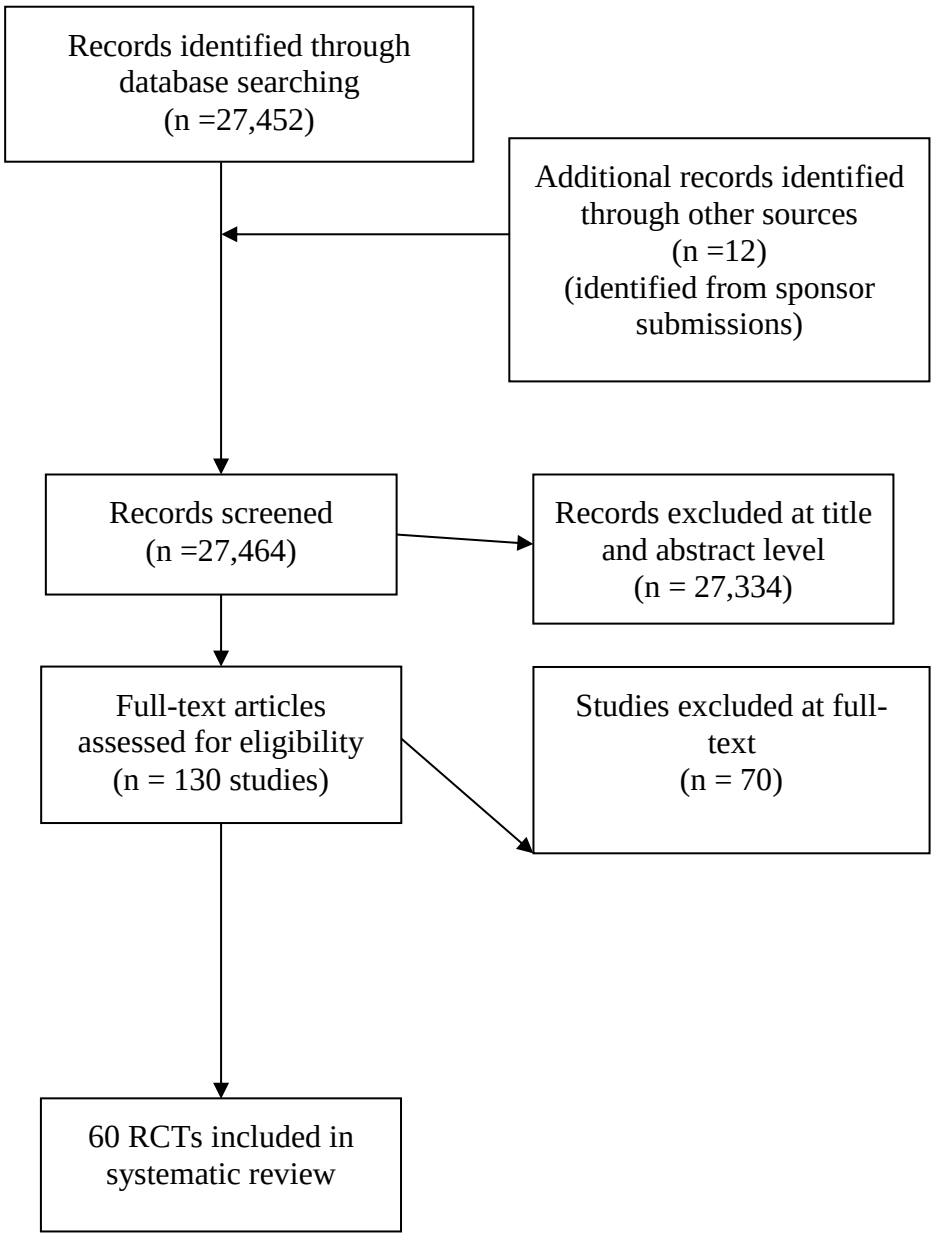
5.2 Results

5.2.1 Quantity and quality of research available

5.2.1.1 Quantity of research available

As a result of the searches described in Section 5.1., a total of 43,764 citations were identified for the review of clinical effectiveness and safety. This was reduced to 27,464 following deletion of duplicate citations. The study selection process is represented as a PRISMA diagram (Figure 2). A total of 27,334 citations were excluded at title and abstract levels (1606 being non-English language records). Of the remaining records, a total of 60 studies were included in the review. Studies excluded at full text are presented (with rationale for exclusion) in Appendix 2.

Figure 2: Flow diagram of study inclusion (adapted from PRISMA)



RCTs included in the systematic review of clinical effectiveness and network meta-analyses of ACR and EULAR responses are presented below (Table 5) (with MTX-naïve and cDMARD-experienced labels denoting trials included in populations 1 and 2/3 respectively).

Table 5: Trials included in the systematic review and network meta-analyses

Trial (with primary publication details)	Intervention	Population	Included in NMA?
Abe 2006[53]	IFX	cDMARD experienced	Not in NMA (14 week RCT)
ACT-RAY[54]	TCZ	cDMARD experienced	Yes
ADACTA[55]	ADA, TCZ	cDMARD experienced	Yes
ADORE[56,57]	ETN	cDMARD experienced	Not in NMA (16 week study)
AIM [58] [59]	ABT	cDMARD experienced	Yes
AMPLE[60]	ADA, ABT	cDMARD experienced	Yes
APPEAL [61]	ETN	cDMARD experienced	Not in NMA (16 week study)
ARMADA[62]	ADA	cDMARD experienced	Yes
ASPIRE [63]	IFX	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
ASSET[64]	ABT	cDMARD experienced	Not in NMA (4 month RCT)
ASSURE[65]	ABT	cDMARD experienced	Not in NMA (no ACR/EULAR data at 22-30 weeks)
ATTEST[66]	IFX, ABT	cDMARD experienced	Yes
ATTRACT[67]	IFX	cDMARD experienced	Yes
AUGUST II[68]	ADA	cDMARD experienced	Yes
Bejarano 2008[69,69]	ADA	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
BeST [70]	IFX	MTX-naive	Yes
CERTAIN[71]	CTZ	cDMARD experienced	Yes
CHANGE[72]	ADA	cDMARD experienced	Yes
COMET [73]	ETN	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
DE019 [74]	ADA	cDMARD experienced	Yes
DeFilippis 2006[75]	ETN, IFX	cDMARD experienced	Yes
Durez 2004 [76]	IFX	cDMARD experienced	Not in MTC (14 week study, no valid comparator arm)
Durez 2007[76]	IFX	MTX-naive	Yes
ERA[77]	ETN	MTX-naive	Yes
ETN Study 309 [78,79]	ETN	cDMARD experienced	Yes
GO-BEFORE [80]	GOL	MTX-naive	Yes
GO-FORTH[81]	GOL	cDMARD experienced	Yes
GO-FORWARD[82]	GOL	cDMARD experienced	Yes
GUEPARD[83]	ADA	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
HIT HARD[84]	ADA	MTX-naive	Yes
IDEA [85]	IFX	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
IIBCREATE[86]	ETN	cDMARD experienced	Yes
JESMR [87]	ETN	cDMARD experienced	Yes

Trial (with primary publication details)	Intervention	Population	Included in NMA?
Kay 2008[88]	GOL	cDMARD experienced	Not in NMA (no eligible ACR/EULAR data at 22-30 weeks (due to PBO group crossover))
Kim 2007[89]	ADA	cDMARD experienced	Yes
Kume 2011 [90]	ADA, ETN	MTX-naive	Not in NMA (early escape at 12 weeks with no imputation for missing data)
Lan 2004[91]	ETN	cDMARD experienced	Not in NMA (12 week study)
LARA[92]	ETN	cDMARD experienced	Yes
MEASURE[93]	TCZ	cDMARD experienced	Not in NMA (no ACR/EULAR data at 22-30 weeks)
Moreland 1999[94 95]	ETN	cDMARD experienced	Yes
Nishimoto 2004[96]	TCZ	cDMARD experienced	Not in NMA (no ACR/EULAR data at 22-30 weeks)
OPERA [97]	ADA	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
OPTIMA[98]	ADA	MTX-naive	Yes
PREMIER [99]	ADA	MTX-naive	Yes
Quinn 2005 [100]	IFX	MTX-naive	Not in NMA (no ACR/EULAR data at 22-30 weeks)
RACAT [101 102]	ETN	cDMARD experienced	Yes
REALISTIC[103]	CTZ	cDMARD-experienced	Not in NMA (no biologic-naïve ACR/EULAR data at 22-30 weeks)
RED-SEA[104]	ADA, ETN	cDMARD experienced	Not in NMA (no ACR/EULAR data at 22-30 weeks)
SAMURAI[105]	TCZ	cDMARD experienced	Yes
SATORI[106]	TCZ	cDMARD experienced	Yes
STAR[107]	ADA	cDMARD experienced	Yes
START [108]	IFX	cDMARD experienced	Yes
Swefot[109]	IFX	cDMARD experienced	Yes
[redacted]	[redacted]	[redacted]	[redacted]
TOWARD[111]	TCZ	cDMARD experienced	Yes
van de Putte 2004[112]	ADA	cDMARD experienced	Yes
Wajdula 2000[113]	ETN	cDMARD experienced	Not in NMA (12 week study)
Weinblatt 1999[114 115]	ETN	cDMARD experienced	Yes
Wong 2009[116]	IFX	cDMARD experienced	Not in NMA (no ACR/EULAR data at 22-30 weeks)
Zhang 2006[117]	IFX	cDMARD experienced	Not in NMA (18 week study)

Sixty RCTs were included in the systematic review of clinical effectiveness. These comprised six trials with head-to-head comparisons of included biologic interventions, [redacted], and 53 trials of biologic interventions compared with placebo (PBO) or cDMARDs.

MTX-naïve trial populations are considered separately in the following results section as population 1. For population 1 there were a total of 15 RCTs included in the systematic review (abatacept N=0, adalimumab N=6, certolizumab pegol N=0, etanercept N=2, golimumab N=1, infliximab N=5, tocilizumab N=0, and head to head biologics N=1). Seven of the MTX-naïve trials had data available for the MTC. All these seven provided ACR data and one of these trials also contributed EULAR data for analysis. A head-to-head trial of adalimumab vs. etanercept was identified but this trial was not eligible for the NMA (due to early escape at 12 weeks with no imputation for missing data).[90]

There were 45 trials with cDMARD-experienced populations (considered as populations 2/3) (abatacept N=3, adalimumab N=7, certolizumab pegol N=2, etanercept N=11, golimumab N=3, infliximab N=7, tocilizumab N=6, head to head biologics N=5, and [redacted]). Of these, 30 trials had data available for the NMA.

Twelve trials which did not satisfy the inclusion criteria for the systematic review (as outlined in Section 5.1) were excluded from the systematic review but were used as additional evidence and explored in sensitivity analyses in the NMA. Of these, ten trials had populations with a small proportion that had received prior biologics (≤ 20%). The other remaining trials were not in the base case because they had populations in which some patients were MTX-naive or cDMARD and others were not, or patients were responding to MTX.

In addition, two trials providing supplementary network linkages were included in the NMA. These RCTs did not include any of the included interventions as specified in the decision problem, but evaluated tofacitinib vs. PBO (Kremer 2012,[118] van der Heijde [119]). Both these trial populations had some prior biologic use (and therefore these trials were considered within the NMA sensitivity analyses).

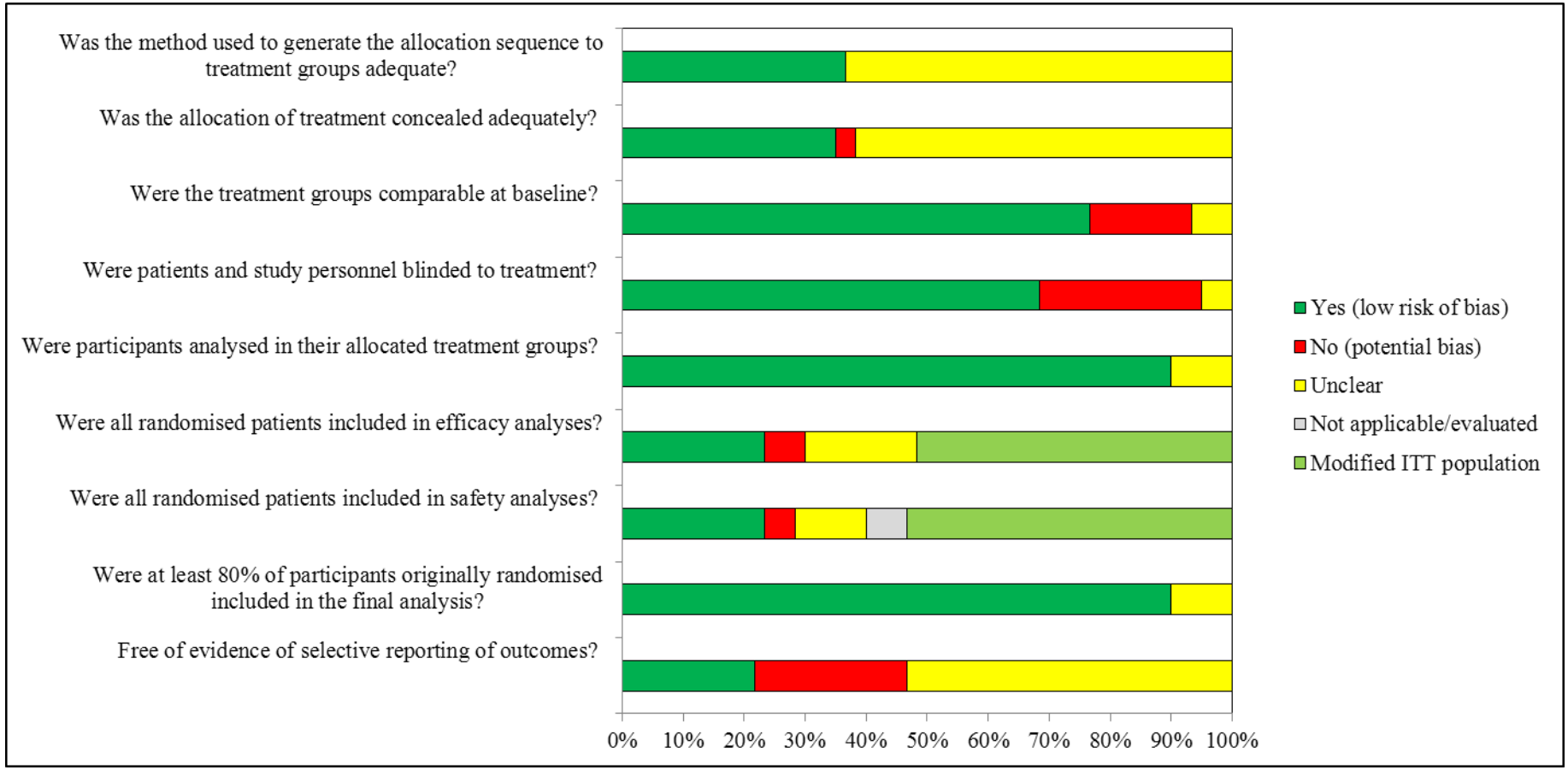
Table 6: Trials not eligible for the systematic review but providing additional evidence for NMA sensitivity analyses

Trial (with primary publication details)	Intervention	Allocated population	Rationale for ineligibility in systematic review
ACQUIRE[120]	ABT	cDMARD experienced	3.4-6% prior biologics
AMBITION[121,121,122]	TCZ	cDMARD experienced	5-9% prior biologics, mix of MTX naïve and prior MTX
JRAPID[123]	CTZ	cDMARD experienced	16% prior biologics
LITHE[124]	TCZ	cDMARD experienced	11% prior biologics
NCT00254293[125]	ABT	cDMARD experienced	2.6% prior biologics
OPTION[126]	TCZ	cDMARD experienced	5-9% prior biologics
ORAL Standard[127]	ADA	cDMARD experienced	10% prior biologics
RA0025[128]	CTZ	cDMARD experienced	15% prior biologics
RAPID1[129]	CTZ	cDMARD experienced	4% prior biologics
RAPID2[130]	CTZ	cDMARD experienced	1.6% prior biologics
TEAR [131]	ETN	cDMARD experienced	Mix of MTX-naive and prior MTX, some patients (fewer than 30%) had any prior cDMARD use
TEMPO[132]	ETN	cDMARD experienced	Mix of MTX-naive, and prior MTX but not inadequate response

5.2.1.2 Quality of research available

The quality of the included RCTs is presented in Table 343 (Appendix 2) and summarised in Figure 3. There is a reasonably low risk of bias overall among studies included in this review. Items where risk of bias was greatest were those that assessed comparability of groups, blinding and selective reporting. Items generating a large proportion of 'unclear' responses (indicating a lack of clarity in reporting) were those relating to generation of allocation sequence, allocation concealment and selective reporting of outcomes. Items with a low risk of bias in a large proportion of trials were comparability at baseline, blinding, analysis by allocated treatment group and most (≥80%) participants randomised included in the final analysis. A modified intention to treat (mITT) population was used in around half of trials for efficacy and safety analyses (which was typically based on all randomised patients who received at least 1 dose of study drug being included in analyses).

Figure 3: Risk of bias graph



5.2.2 Summary of trials and population characteristics

There were some differences between trials in population characteristics, treatment and trial duration. For some trials, intervention and control arms differed in terms of numbers /combinations of concomitant cDMARDs. Some trials allowed physician discretion in other therapies. There was some variation between trials in prior treatment history and disease duration. There was some variation in how early withdrawals were decided, with variation in length of time on allocated treatment.

5.2.2.1 Trial characteristics

Adults with severe active RA not previously treated with MTX (population 1)

As discussed in Section 5.1., trials in which populations were MTX-naïve but had received some prior treatment with other cDMARDs were considered appropriate for inclusion in population 1. Study characteristics for trials included in population 1 are presented in Tables 344 to 345 (Appendix 2).

Adults with moderate to severe and severe active RA that have been previously treated with cDMARDs (but not bDMARDs) (cDMARD-experienced) (populations 2 and 3)

Study characteristics for trials included in populations 2 and 3 are presented in Tables 346 to 348 (Appendix 2)

5.2.2.2 Population characteristics

Adults with severe active RA not previously treated with MTX (population 1)

Population characteristics for population 1 are presented below (Tables 7 to 8).

Adults with moderate to severe and severe active RA that have been previously treated with cDMARDs (but not bDMARDs) (cDMARD-experienced) (populations 2 and 3)

Population characteristics for populations 2 and 3 are presented below (Tables 9 to 10).

Table 7: Population characteristics: Population 1 biologic head to head RCTs

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
Kume 2011 [90]	ADA mon n=22	63 (17)	85.7%	Yes	0.75 (0.42)	5.34 (1.4) ESR
	ETN mon n=21	51 (15)	85.7%		0.92 (0.42)	5.17 (1.5) ESR

Table 8: Population characteristics: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
Bejarano 2008[69]	PBO+MTX n=73	47(9)	53.4	Yes	6.6	6.0(1.5)
	ADA+MTX n=75	47(9)	58.4		7.9	5.9 (1.4)
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy [d] based on DAS28 n=32	49.3 (SD15.2)	81.25%	Yes	4.4 (3.3–5.1) [a] months	(ESR) 6.15 (SD0.88) (CRP) 5.85 (SD0.91)
	Initial ADA+MTX 12 weeks, then step-up [d] therapy based on DAS28 n=33	46.3 (SD16.3)	78.79%		4.4 (3.3–5.1) [a] months	(ESR) 6.31 (SD0.78) (CRP) 5.80 (SD0.83)
HIT HARD[84]	MTX + PBO n=85	52.5 (14.3)	67.1	NR	0.13 (NR)	6.3 (0.9) ESR
	ADA + PBO n=87	47.2 (12.1)	70.1		0.15 (NR)	6.2 (0.8) ESR
OPERA [97]	MTX + PBO + steroid n=91	5.42 (28.3-76.7) [b]	69	Yes	0.22 (0.12-0.41) [b]	5.6 (3.8-7.3) CRP [b]
	ADA + MTX + steroid n=89	56.2 (25.8-77.6) [b]	63		0.24 (0.12-0.44) [b]	5.5 (3.8-7.8) CRP [b]
OPTIMA	MTX + PBO n=517	50.7 (NR)	74	NR	0.38 (NR)	6
	ADA + MTX n=515	50.4 (NR)	74		0.30 (NR)	6
PREMIER	MTX + PBO n=257	52.0 (13.1)	73.9	Yes	0.8 (0.9)	6.3 (0.9)
	ADA mon + PBO step up week 16	52.1 (13.5)	77.4		0.7 (0.8)	6.4 (0.9)

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
	n=274					
	ADA + MTX step up week 16 n=268	51.9 (14.0)	72.0		0.7 (0.8)	6.3 (0.9)
COMET	MTX +PBO n=268	52·3 (SD 0·8)	73%	NR	months 9.3 (SD0.4)	6.5 (SD1.0)
	ETN+MTX n=274	50·5 (SD 0·9)	74%		months 8.8 (SD0.4)	6.5 (SD1.0)
ERA, Bathon 2000 Multicentre	MTX + PBO n=217	49 (13)	75	NR	1 (0.92)	NR
	ETN + PBO n=207	50 (13)	74		1 (0.92)	NR
GO-BEFORE	PBO+MTX n=160	48.6 (12.91)	(83.8	NR	≤ 3 years = 72.5% ≤ 2 years = 61.9% ≤ 1 years = 45.6%	ESR= 6.2 (1.17) CRP= 5.6 (1.06)
	GOL + MTX n=159	50.9 (11.32)	84.9		≤ 3 years = 73.0% ≤ 2 years = 64.2% ≤ 1 years = 50.9%	ESR= 6.3 (1.11) CRP= 5.7 (1.05)
ASPIRE	PBO i.v. + MTX n=298	50 (13)	75	NR	0.9 (0.7)	NR
	IFX + MTX n=273	51 (12)	71		0.8 (0.7)	NR
BeST	Sequential monotherapy (DAS-steered) n=126	54 (13)	68	Yes	23 weeks [c]	DAS44 = 4.5 (0.9)
	Step-up combination therapy (DAS-steered) n=121	54 (13)	71		26 weeks [c]	DAS44 = 4.5 (0.8)
	Initial combination therapy with prednisone (DAS-steered) n=133	55 (14)	65		23 weeks [c]	DAS44 = 4.4 (0.9)
	Initial combination therapy with IFX (DAS-steered) n=128	54 (14)	66		23 weeks [c]	DAS44 = 4.3 (0.9)
Durez 2007	MTX n=14	53.8 (15.2)	71%	NR	0.45 (0.29)	CRP 5.2 (0.8)
	MTX +MP n=15	50.3 (14.2)	60%		0.25 (0.33)	5.3 (1.3)
	IFX +MTX n=15	50.0 (9.9)	67%		0.36 (0.31)	5.3 (1.1)

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
IDEA	MP + MTX n=112 across both groups	NR	NR	Yes	NR (described as early RA, 3-12 months symptom duration)	NR
	IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22 + MTX (IFX dose modifications permitted according to DAS44 from week 26)	NR	NR			NR
Quinn 2005	MTX + PBO n=10	53.1 (13.7)	70%	NR	0.5 (0.31)	7.0 (0.9)
	IFX + MTX n=10	51.3 (9.5)	60%		0.62 (0.38)	6.2 (0.8)

[a] = *Median (IQR)*
[b] = *Median (5th, 95th centile range)*
[c] = *Median*
[d] = *more details in trial characteristics table in appendix*

Table 9: Population characteristics: Population 2/3 biologic head to head RCTs

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
ATTEST[66]	PBO+MTX n=110	49.4 (11.5)	87.3	NR	8.4 (8.6)	ESR 6.8 (1.0)
	IFX + MTX n=165 [a]	49.1 (12.0)	82.4		7.3 (6.2)	6.8 (0.9)
	ABT + MTX n=156 [b]	49.0 (12.5)	83.3		7.9 (8.5)	6.9 (1.0)
AMPLE	ABT s.c. n=318	51.4	81.4	NR	1.9	5.5 (CRP)
	ADA n=328	51.0	82.3		1.7	5.5 (CRP)
RED-SEA[104]	ADA+cDMARDs n=60	55.0	75	NR	7.0 (range3.3–13.0)	5.6
	ETN50+cDMARDs n=60	53.2	70		5.5 (range2.0–14.5)	5.8
ADACTA[55]	TCZ + PBO n=163	54.4 (13.0)	79	Yes	7.3 (8.1)	6.7 (0.9)
	ADA + PBO n=163	53.3 (12.4)	82		6.3 (6.9)	6.8 (0.9)
DeFilippis 2006 24623 [133]	ETN + MTX n=16	44.7 (14.17)	NR	NR	NR	NR
	IFX + MTX n=16	46.79 (10.9)	NR		NR	NR

[a] = IFX 3 mg/kg i.v. administered on days 1 (i.e. week 0), 15 (i.e. week 2), 43 (i.e. week 6) and 85 (i.e. week 12) and every 56 days (i.e. 8 weeks) thereafter(NB: licensed dose 3 mg/kg i.v. at weeks 0, 2, 6 and every weeks thereafter, adjustments in dosage and frequency of administration permitted after week 12 in license)
+ MTX

[b] = ABT dosed according to weight: patients weighing less than 60 kg, 60-100kg, or more than 100kg received 500 mg, 750 mg or 1000 mg of ABT respectively. ABT administered i.v. on days 1, 15 and 29 and every 28 days thereafter, up to and including day 337+ MTX

Table 10: Population characteristics: Population 2/3 (cDMARD experienced) vs. cDMARD(s) or PBO

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
AIM	MTX+PBO n=219	50.4	81.7	NR	8.9 (7.1)	6.4 (0.1)CRP
	ABTi.v.+ MTX n=433	51.5	77.8		8.5 (7.3)	6.4 (0.08) CRP
ASSET	PBO + MTX n=23	52.5 (11.5)	69.6	NR	2.4 (1.4)	5.3 (0.9) CRP
	ABT i.v. (~10mg/kg) + MTX n=27	51.7 (11.2)	59.3		2.1 (1.5)	5.3 (1.1) CRP
ASSURE	PBO + cDMARDs n=482	52.0 (12.1)	83.7	NR	9.5 (9.1)	NR
	ABT + cDMARDs n=959	52.2 (11.8)	83.1		9.5 (8.7)	NR
AUGUST II	MTX+PBO n=76	54	84	NR	8.4	5.8
	ADA+MTX n=79	53	81		8.8	5.8
CHANGE	PBO n=87	53.4	77	Yes	8.4	NR
	ADAmon n=91	56.9	79.1		9.9	NR
DE019	MTX+PBO n=200	56.1	73	Yes	10.9	NR
	ADA+MTX n=207	56.1	76.3		11	NR
STAR	PBO+cDMARDs n=318	55.8	79.2	NR	11.5	NR
	ADA+cDMARDs n=318	55	79.6		9.3	NR
van de Putte 2004	PBO s.c. n=110	53.5 (13.2)	77.3	Yes	11.6 (9.3)	7.09 (0.87)
	ADA mon n=113	52.7 (13.3)	79.6		10.6 (6.9)	7.07 (0.86)
ARMADA	MTX+PBO n=62	56	82.3	Yes	11.1	NR

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
	ADA+MTX n=67	57.2	74.6		12.2	NR
Kim 2007	MTX+PBOrescueWeek18 n=65	49.8	85.7	Yes	6.9	NR
	ADA+MTX n=63	48.5	95.4		6.8	NR
CERTAIN	PBO + cDMARDs n=98	54.0 (12.4)	76.5	Yes	4.7 (3.3)	4.47 (0.34) ESR
	CTZ + DMARDs n=96	53.6 (11.9)	84.4		4.5 (3.5)	4.53 (0.43) ESR
REALISTIC	PBO + existing cDMARDs (biologic naive subgroup) n=29	NR (overall trial pop 53.9 (12.7) (overall trial pop, n=212)	79.7 (overall trial pop, n=212)	NR No (NA as trial only 12 weeks)	8.9 (9.1) (overall trial pop, n=212)	DAS28-ESR 6.4 (0.9) DAS28-CRP 5.7 (0.9) (overall trial pop, n=212)
	CTZ existing cDMARDs (biologic naive subgroup) n=134	55.4 (12.4) (overall trial pop, n=851)	77.6 (overall trial pop, n=851)		8.6 (8.8) (overall trial pop, n=851)	DAS28-ESR 6.4 (0.9) DAS28-CRP 5.7 (0.9) (overall trial pop, n=851)
ADORE	ETNmon n=159	53	79.2	NR	10.0	6.2
	ETN+MTX n=155	54	76.8		9.8	6.3
CREATEIIb	DMARD+PBO n=65	51.5	83.1	NR	8.2(7.59)	6.3 (0.76)
	ETN50+DMARD n=64	51.2	85.9		7.9(7.15)	6.4 (0.85)
ETN Study 309 (Combe 2006)	SSZ+PBO n=50	53.3	82	NR	5.6	DAS44-ESR 5.0
	ETN+PBO n=103	51.3	78.6		7.1	DAS44-ESR 5.1
	ETN+SSZ n=101	50.6	80.2		6.5	DAS44-ESR 5.2
JESMR	ETN mon n=74	58.1 (12.6)	87.3	NR	10.6 (10.5)	6.1
	ETN + MTX 6-8mg/week n=77	56.5 (11.1)	80.0		8.1 (7.7)	6.0
Lan 2004	PBO+MTX n=29	50.79	90	NR	NR (eligibility more than one year)	NR

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
	ETN+MTX n=29	47.55	83			NR
LARA	MTX+DMARD n=142	48.6	90.1	NR	9.0 (7.5)	5.9
	ETN50+MTX n=281	48.4	88.3		7.9 (7.0)	5.9
Moreland 1999	PBO n=80	51	76	NR	12	NR
	ETN+PBO n=78	53	74		11	NR
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178	57.8 (13)	43.4	Yes	5.5(9.3)	5.8
	ETN50+MTX n=175	56 (13.2)	48.9		4.9(8.0)	5.9
Wajdula 2000 [113]	PBO n=111	53	NR	NA (12 week study)	7.2	NR
	ETN n=105	53	NR		7.5	NR
Weinblatt 1999	MTX +PBO, n=30	53	73	Yes	13	NR
	ETN+ MTX, n=59	48	90		13	NR
APPEAL	MTX plus DMARD (SSZ, HCQ or leflunomide), n=103	48.5 (11.3)	88.4	NR	6.9 (8.5)	ESR 6.1 (1.1) CRP 5.34(1.1)
	ETN+MTX, n=197	48.4(12.0)	91.4		6.5 (7.3)	ESR 6.1 (1.1) CRP 5.23 (1.1)
GO-FORTH	PBO + MTX 6-8mg/week n=90	51.1 (11.6)	83.0	Yes	8.7 (8.2)	5.6 (0.99) ESR
	GOL + MTX 6-8mg/week n=89	50.4 (9.9)	84.9		8.8 (8.8)	5.5 (1.18) ESR
GO-FORWARD	PBO + MTX n=133	Mean (SD) = 51.2 (11.96) 52.0 (42.0 to 58.0) [a]	82.0 (109/133)	Yes	Mean (SD)= 8.62 (7.86) 6.5 (3.1 to 11.9) [a]	CRP 5.458 (4.672 to 6.093) [a] ESR 6.111 (5.260 to 6.574) [a]
	GOL + MTX n=89	Mean (SD)=50.3 (10.98)	80.9 (72/89)		Mean (SD)=7.33 (7.83)	CRP 5.766 (4.628 to 6.322) [a]

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
		52.0 (43.0 to 57.0) [a]			4.5 (2.1 to 9.7) [a]	
Kay 2008	PBO s.c. + MTX n=35	(46.0, 66.0) [a]	74.3%	Yes	5.6 (1.4, 10.9) [a]	CRP 5.8 (5.2, 6.4) [a] ESR 6.3 (5.7, 7.0) [a]
	GOL + MTX n=35	57.0 (50.0, 64.0) [a]	85.7%		8.2 (4.1, 14.3) [a]	CRP 5.9 (5.5, 6.9) [a] ESR 6.4 (5.6, 7.3) [a]
Abe 2006	PBO + MTX n=47	55.1 (7.6)	35/47 (74.5)	NR	7.5 (5.0)	NR
	IFX + MTX n=49	55.2 (10.9)	40/49 (81.6)		9.1 (7.4)	NR
ATTRACT	PBO + MTX n=88	51 (19.0, 75.0) [a]	70/88 (80)	NR	8.9 (0.8, 35.0) [b]	NR
	IFX +MTX n=86	56 (25.0, 74.0) [a]	70/86 (81)		8.4 (0.7, 45.0) [b]	NR
Durez 2004	Single i.v. infusion of MP (sodium hemisuccinate) at week 0 + MTX n=14	56 (35-79) [b]	73%	NR	12 (1-24) [b]	NR
	IFX + MTX n=12	48 (34-60) [b]	100%		10 (2-20) [b]	NR
START	PBO + MTX n=363	52.0 (44-61) [a]	83.2	Yes	8.4 (4-15) [a]	NR
	IFX + MTX n=360	53.0 (45-61) [a]	80.0		7.8 (3-15) [a]	NR
Swefot	SSZ + HCQ + MTX n=130	52.9 (13.9)	101/130 (78)	Yes	0.525	4.79 (1.05)
	IFX+MTX n=128	51.1 (13.3)	97/128 (76)		0.517	4.91 (0.98)
Wong 2009	PBO + MTX (with crossover to open-label IFX at week 24). n=9	50 (16)	8/9	Yes	NR	6.4 (0.8)
	IFX + MTX n=17	48 (12)	14/17		NR	6.2 (0.9)
Zhang 2006	PBO. + MTX n=86	48.9 (8.0)	84.9	NR	8 (6.22)	NR

Trial name / Author, year	Treatment arms	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
	IFX + MTX n=87	47.9 (10.1)	85.1		7.13 (6.17)	NR
ACT-RAY	TCZ + PBO n=277	53.6 (11.9)	78.6	NR	8.3 (8.4)	ESR 6.36 (1.00)
	TCZ + MTX n=276	53.0 (13.4)	81.9		8.2 (8.0)	ESR 6.33 (0.98)
MEASURE	PBO + MTX n=69	NR	NR	Yes	NR	NR
	TCZ + MTX n=69	NR	NR		NR	NR
Nishimoto 2004	PBO n=53	53.0 (31-73) [b]	73.6	NR	8.4 (0.7-52.7) [b]	NR
	TCZ mon n=55	56.0 (25-74) [b]	83.6		8.3 (1.3-45.7) [b]	NR
SAMURAI	cDMARDs n=145	53.1	82	NR	124.8weeks	6.4
	TCZmon n=157	52.9	79.6		114.4weeks	6.5
SATORI	PBO + MTX n=64	50.8 (12.2)	(48/64 evaluated)	NR	8.7 (7.1)	6.2 (0.9)
	TCZ + PBO n=61	52.6 (10.6)	90.2		8.5 (8.4)	6.1 (0.9)
TOWARD	PBO + stable cDMARDs n=415	54 (13)	84	Yes	9.8 (9.1)	6.6 (1.0)
	TCZ + stable DMARDs n=805	53 (13)	81		9.8 (8.8)	6.7 (1.0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [a]	[redacted]
	[redacted]	[redacted]	[redacted]		[redacted] [a]	[redacted]

[a] = *median (IQR)*
[b] = *median (range)*

Additional population characteristics are outlined in Tables 349 to 354 (Appendix 2).

5.2.3 Assessment of effectiveness

5.2.3.1 Disease activity and physical function

ACR response

Population 1

One head-to-head RCT in MTX-naïve patients was identified in the systematic review.[90] However, no ACR response data were available in this trial. A total of 12 RCTs of biologic vs. DMARD(s) or PBO reported ACR response data in MTX-naïve patients (5 for adalimumab, 2 for etanercept, 1 for golimumab, and 4 for infliximab) (Table 11). Statistically significant differences in ACR response favouring biologic treatment over comparator were reported for adalimumab (4 studies), etanercept (2 studies), golimumab (1 study) and infliximab (2 studies). Seven of the 12 RCTs contributed data to a NMA of ACR response for population 1 (3 for adalimumab, 1 for etanercept, 1 for golimumab, and 2 for infliximab).

(NB: In the outcome tables that follow throughout Section 5.2., citations are provided where data were extracted from sources additional to the primary publication).

Table 11: ACR response data: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	12 weeks	32	50	27	19	N
	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28	12 weeks	33	84	66	44	
GUEPARD	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	52 weeks	32	81	68	58	N
	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28	52 weeks	33	85	67	42	
HIT HARD[84]	PBO + MTX	24 weeks	85	67.6	48.7	26.8	Y
	ADA + MTX	24 weeks	87	79.0	63.8	48.0 [a]	
OPERA [97]	PBO + MTX + steroid	12 months	91	78	63	45	N
	ADA + MTX + steroid	12 months	89	86	80 [a]	65 [a]	
OPTIMA [134]	PBO + MTX	26 weeks	517	57	34	17	Y
	ADA + MTX	26 weeks	515	70 [b]	52 [b]	35 [b]	
PREMIER (supplementary data identified via Clinicaltrials.gov)	PBO + MTX	26 weeks	257	61.5	40.5	22.2	Y
	ADA mon + PBO	26 weeks	274	53.3	35.0	19.7	
	ADA + MTX	26 weeks	268	68.7	58.6	42.5	
PREMIER	PBO + MTX	1 year	257	63	46	28	N
	ADA mon + PBO	1 year	274	54 [a (vs. MTX mon)]	41	26	
	ADA + MTX	1 year	268	73 [a (vs. MTX mon), b (vs. ADA mon)]	62 [b]	46 [b]	
PREMIER	PBO + MTX	2 years	257	56	43	28	N
	ADA mon + PBO	2 years	274	49	37	28	
	ADA + MTX	2 years	268	69 [a (vs. MTX mon), b (vs. ADA mon)]	59 [b]	47 [b]	

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
COMET	PBO + MTX	52 weeks	268	67	49	28	N
	ETN+MTX	52 weeks	274	86	71	48 [b]	
COMET [135]	MTX in year 1, MTX in year 2	2 years (week 104)	99	61	46	32	N
	MTX year 1, ETN + MTX in year 2	2 years (week 104)	90	81 [a]	66 [a]	48 [a]	
	ETN + MTX in year 1, ETN + MTX in year 2	2 years (week 104)	111	86 [a]	70 [a]	57 [b]	
	ETN + MTX in year 1, ETN in year 2	2 years (week 104)	111	80	64	44	
ERA	PBO + MTX	6 months	217	58.2	31.54	14.24	Y
	ETN + PBO	6 months	207	65.42	40.14	20.94 [a]	
ERA	PBO + MTX	12 months	217	66 [c]	44 [c]	23 [c]	N
	ETN + PBO	12 months	207	72 [c]	49 [c]	26 [c]	
GO-BEFORE	PBO + MTX	24 weeks	160	49.4	29.4	15.6	Y
	GOL + MTX	24 weeks	159	61.6 [a]	40.3 [a]	23.9	
GO-BEFORE [136]	PBO + MTX	52 weeks	160	63.1	40.6	24.4	N
	GOL + MTX	52 weeks	159	68.6	43.4	28.3	
ASPIRE	PBO + MTX	54 weeks	274	53.6	32.1	21.2	N
	IFX + MTX	54 weeks	351	62.4 [a]	45.6 [b]	32.5 [a]	
BeST	Sequential monotherapy	6 months	126	49.69	NR	15.9	Y
	Step-up combination therapy	6 months	121	60.04	NR	11.77	
	Initial combination therapy + prednisone	6 months	133	70.63	NR	26.58	
	Initial combination therapy + IFX	6 months	128	74.3	NR	31.15	
Durez 2007	MTX	22 weeks	14	28.13	7.69	0	Y
	MTX + i.v. MP	N/A	N/A	N/A	N/A	N/A	
	IFX + MTX	22 weeks	15	86.72 [a]	66.85 [a]	33.79 [a]	
Durez 2007	MTX	52 weeks	14	46 [c]	39 [c]	14 [c]	N
	MTX + i.v. MP	52 weeks	15	87 [c]	67 [c]	53 [c]	
	IFX + MTX	52 weeks	15	80 [c]	65 [c]	29 [c]	

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
Quinn 2005	PBO + MTX	14 weeks	10	20	0	0	N
	IFX + MTX	14 weeks	10	60	60	60	
Quinn 2005	PBO + MTX	54 weeks	10	60	40	30	N
	IFX + MTX	54 weeks	10	80	80	70	

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *estimated from graphical data*

Population 2/3

Four head to head RCTs reporting ACR response data in cDMARD-experienced patients were identified (Table 12). Statistically significantly greater proportions of patients achieved ACR20, ACR50 and ACR70 responses in the infliximab plus methotrexate and abatacept i.v. plus methotrexate treatment groups of the ATTEST trial[66] when compared against placebo plus methotrexate. Statistically significant findings were also identified in the ADACTA trial, whereby greater proportions of patients receiving tocilizumab monotherapy achieved ACR responses than among patients receiving adalimumab monotherapy.[55] Thirty six RCTS evaluating biologic vs. DMARD(s) or PBO in cDMARD-experienced patients reported ACR response data. Statistically significant findings were reported (4 adalimumab trials, 1 certolizumab pegol trial, 8 etanercept trials, 3 golimumab trials, 5 infliximab trials and 4 tocilizumab trials) for ACR response across a range of time points favouring biologic over comparator treatment.

Table 12: ACR response data: Population 2/3 biologic head to head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Numbers analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
ATTEST	PBO + MTX	Day 197	110	41.8	20	9.1	Y
	IFX + MTX	Day 197	165	59.4 [a vs. PBO]	37 [a vs. PBO]	24.2 [a vs. PBO]	
	ABT i.v. + MTX	Day 197	156	66.7 [b vs. PBO]	40.4 [b vs. PBO]	20.5 [a vs. PBO]	
AMPLE	ABT s.c.	28 weeks (197 days)	328	66.13	45.7	24.19	Y
	ADA	28 weeks (197 days)	318	64.52	42.47	22.58	
AMPLE	ABT s.c.	1 year	328	64.8	46.2	29.2	N
	ADA	1 year	318	63.4	46	26.2	
ADACTA	TCZ + s.c. PBO	24 weeks	163	65.0 [a]	47.2 [a]	32.5 [a]	Y
	ADA + i.v. PBO	24 weeks	162	49.4	27.8	17.9	
De Filippis 2011	ETN + MTX	22 weeks	15	60	26	7	Y
	IFX + MTX	22 weeks	15	60	33	7	
De Filippis 2011	ETN + MTX	54 weeks	15	74	53	7	N
	IFX + MTX	54 weeks	15	60	19	20	

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *estimated from graphical data*

Table 13: ACR response data: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Numbers analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
AIM [59]	PBO + MTX	6 months	219	39.7	16.8	6.5	Y
	ABT i.v.+ MTX	6 months	433	67.9	39.9	19.8	
AIM	PBO + MTX	12 months	219	39.7	18.2	6.1	N
	ABT i.v.+ MTX	12 months	433	73.1	48.3	28.8	
AUGUST II	PBO + MTX	26 weeks	76	46	15	5	Y
	ADA + MTX	26 weeks	79	71 [b]	38 [b]	18 [a]	
CHANGE	PBO	24 weeks	87	13.8	5.7	1.1	Y
	ADA mon	24 weeks	91	44	24.2	12.1	
DE019	PBO + MTX	24 weeks	200	29.5	9.5	2.5	Y
	ADA + MTX	24 weeks	207	63.3	39.1	20.8	
DE019	PBO + MTX	52 weeks	200	24.0	9.5	4.5	N
	ADA + MTX	52 weeks	207	58.9 [b]	41.5 [b]	23.2 [b]	
STAR	PBO + cDMARDs	24 weeks	318	34.9	11.3	3.5	Y
	ADA + cDMARDs	24 weeks	318	52.8 [a]	28.9 [a]	14.8 [a]	
van de Putte 2004	PBO s.c.	26 weeks	110	19.1	8.2	1.8	Y
	ADA mon	26 weeks	113	46.0 [b]	22.1 [a]	12.4 [a]	
ARMADA	PBO + MTX	24 weeks	62	14.5	8.1	4.8	Y
	ADA + MTX	24 weeks	67	67.2	55.2	26.9	
Kim 2007	PBO + MTX	24 weeks	63	36.5	14.3	7.9	Y
	ADA + MTX	24 weeks	65	61.5	43.1	21.5	
CERTAIN	PBO + cDMARDs	24 weeks	98	16.3	8.2	3.1	Y
	CTZ + DMARDs	24 weeks	96	36.5 [a]	20.8 [a]	9.4	
REALISTIC	PBO + existing cDMARDs	12 weeks	29	20.7	NR	NR	N
	CTZ + existing cDMARDs	12 weeks	134	54.5	NR	NR	
ADORE van Riel 2006	ETN mon	16 weeks	155	71.0	41.9	17.4	N
	ETN + MTX	16 weeks	152	67.1	40.1	18.4	
CREATE IIb [86 137]	PBO + DMARD	24 weeks	65	32.3	16.9	4.6	Y
	ETN50 + DMARD	24 weeks	64	65.6	46.9	23.4	
ETN309	PBO + SSZ	24 weeks	50	28.0	14.0	2.0	Y
	ETN + PBO	24 weeks	103	73.8	46.6	21.4	

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Numbers analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
				a vs. SSZ			
	ETN + SSZ	24 weeks	101	74.0 a vs. SSZ, NS vs. ETN+PBO	52.0 a vs. SSZ, NS vs. ETN+PBO	25.0 a vs. SSZ, NS vs. ETN+PBO	
ETN309 Coombe 2009[79]	PBO + SSZ	104 weeks	50	34	10 [c]	2 [c]	N
	ETN + PBO	104 weeks	103	67 [a vs. SSZ]	45 [a vs. SSZ, c]	24 [a vs. SSZ, c]	
	ETN + SSZ	104 weeks	101	77 [a vs. SSZ]	58 [a vs. SSZ, c]	27 [a vs. SSZ, c]	
JESMR	ETN mon	24 weeks	69	63.8	47.8	26.1	Y
	ETN + MTX	24 weeks	73	90.4 [b]	64.4	38.4	
JESMR [138]	ETN mon	52 weeks	69	63.8	43.5	29	N
	ETN + MTX	52 weeks	73	86.3 [b]	76.7 [b]	50.7 [a]	
Lan 2004	PBO + MTX	12 weeks	29	34	10	0	N
	ETN + MTX	12 weeks	29	90 [b]	66 [b]	24	
LARA	MTX + DMARD	24 weeks	142	50	23.2	11.3	Y
	ETN50 + MTX	24 weeks	279	83.2 [b]	62 [b]	34.8 [b]	
Moreland 1999 [94 95]	PBO	3 months	80	23	8	4	N
	ETN + PBO	3 months	78	62 [b]	41 [b]	15 [a]	
Moreland 1999 [94 95]	PBO	6 months	80	11	5	1	Y
	ETN + PBO	6 months	78	59 [b]	40 [b]	15 [b]	
RACAT	MTX + SSZ + HCQ	24 weeks	159	55.97	25.79	5.03	Y
	ETN50 + MTX	24 weeks	163	55.21	35.58	15.95 [a]	
RACAT	MTX + SSZ + HCQ In analysis n=154 (of whom 39 switched to ETN)	48 weeks	154	57.4	35.5	18.1	N
	ETN50 + MTX n=175 In analysis n=155 (of whom 41 switched to MTX+SSZ+HCQ)	48 weeks	155	65.8	42.6	26.5	
Wajdula 2000 [113]	PBO	12 weeks	100	12%	NR	NR	N

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Numbers analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
Wajdula 2000	ETN	12 weeks	109	70%	NR	NR	
Weinblatt 1999	PBO + MTX	24 weeks	30	27	3	0	Y
	ETN + MTX	24 weeks	59	71 [b]	39 [b]	15 [a]	
APPEAL	MTX + DMARD (SSZ, HCQ or LEF)	16 weeks	103	58	35	7	N
	ETN + MTX	16 weeks	197	79 [b]	57 [b]	19 [a]	
GO-FORTH	PBO + MTX	14 weeks	88	27.3	9.1	2.3	N
	GOL + MTX	14 weeks	86	72.1 [b]	43.0 [b]	22.1 [b]	
GO-FORTH	PBO + MTX	24 weeks	88	33.0	14.8	5.7	Y
	GOL + MTX	24 weeks	86	70.9 [b]	41.9 [b]	26.7 [b]	
GO-FORWARD	PBO + MTX	14 weeks	133	33.1	9.8	3.8	N
	GOL + MTX	14 weeks	89	55.1 [b]	34.8 [b]	13.5 [a]	
GO-FORWARD	PBO + MTX	24 weeks	133	27.8	13.5	5.3	Y
	GOL + MTX	24 weeks	89	59.6 [b]	37.1 [b]	20.2 [b]	
Kay 2008	PBO + MTX	16 weeks	35	37.1	5.7	0	N
	GOL + MTX	16 weeks	35	60.0	37.1 [b]	8.6	
Abe 2006	PBO + MTX	14 weeks	47	23.4	8.5	0	N
	IFX + MTX	14 weeks	49	61.2	30.6	10.2	
ATTRACT	PBO + MTX	30 weeks	84	22.34	5	0	Y
	IFX + MTX	30 weeks	83	53.79	27 [b]	8 [a]	
ATTRACT Lipsky *et al.*, 2000 [139]	PBO + MTX	54 week	88	17	8	2	N
	IFX + MTX	54 week	86	42 [b]	21 [a]	10 [a]	
Durez 2004	MP i.v. + MTX	14 weeks	12	8	0	0	N
	IFX + MTX	14 weeks	9	67 [a]	44 [a]	0	
Swefot	SSZ + HCQ + MTX	12 months after study inclusion	130	28	15	7	N

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Numbers analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
		(8-9 months (35-39 weeks) after randomisation)					
	IFX + MTX	12 months after study inclusion (8-9 months (35-39 weeks) after randomisation)	128	42 [a]	25 [a]	12	
Swefot [140]	SSZ + HCQ + MTX	24 months after study inclusion (20-21 months (87-91 weeks) after randomisation)	130	33	22	14	N
	IFX + MTX	24 months after study inclusion (20-21 months (87-91 weeks) after randomisation)	128	40	30	16	
START	PBO + MTX	22 weeks	363	25.5	9.7	4.7	Y
	IFX + MTX	22 weeks	360	58.0 [b]	32.1 [b]	14.0 [b]	
Zhang 2006	PBO + MTX	18 weeks	NR (86 randomised)	48.84	25.58	13.95	N
	IFX + MTX	18 weeks	NR (87 randomised)	75.86 [b]	43.68 [a]	22.99	
ACT-RAY	TCZ + oral PBO	24 weeks	276	70.3	40.2	25.4	Y
	TCZ + MTX	24 weeks	277	71.5	45.5	24.5	
MEASURE	PBO + MTX	12 weeks	NR	25	6	3	N
	TCZ + MTX	12 weeks	NR	51	17	10	
Nishimoto 2004	PBO	12 weeks	53	11.3	1.9	0	N
	TCZ	12 weeks	55	78.2 [b]	40.0 [b]	16.4 [a]	
SAMURAI	cDMARDs	24 weeks	145	38.67	17.64	6.86	Y
	TCZ	24 weeks	157	82.06	57.27	33.82	
SAMURAI	cDMARDs	52 weeks	145	34	13	6	N
	TCZ	52 weeks	157	78 [b]	64 [b]	44 [b]	
SATORI	PBO + MTX	24 weeks	64	25	16.86	10.97	Y
	TCZ + PBO capsules	24 weeks	61	80.3 [b]	54.44	33.19	
TOWARD	PBO + stable cDMARDs	24 weeks	413	24.5	9	2.9	Y
	TCZ + stable DMARDs	24 weeks	803	60.8 [b]	37.6 [b]	20.5 [b]	

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *estimated from graphical data*

EULAR response

Population 1

The only head-to-head trial for methotrexate-naive patients (Kume 2011 [90]) did not report EULAR data. Three methotrexate-naive trials reported EULAR data, of which two were adalimumab trials (GUEPARD[83], OPERA [97]), and one was a golimumab trial (GO-BEFORE[80]) (Table 14 EULAR Population 1 vs DMARD(s) or placebo). GUEPARD[83] reported a significantly better EULAR response for adalimumab plus methotrexate compared with methotrexate alone at 12 weeks follow-up, but at one year follow-up when both groups had undergone step-up therapy, both groups were responding similarly well. OPERA [97] reported similar EULAR responses for adalimumab plus methotrexate plus steroid and for methotrexate plus placebo plus steroid at one year follow-up. GO-BEFORE, at 24 weeks, reported a significantly better EULAR response for golimumab plus methotrexate and for placebo plus methotrexate but at one year follow-up both groups were doing similarly well. GO-BEFORE contributed EULAR data to the NMA, whereas the others did not report data within 22-30 weeks follow-up.

Table 14: EULAR response: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving no EULAR response	% achieving moderate EULAR response	% achieving good EULAR response	% EULAR responder (moderate/good)	In NMA?
GUEPARD[83]	MTX	week 12	32	NR	NR	25	NR	No
	ADA+MTX	week 12	33	NR	NR	63.6 [a]	NR	No
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy	week 52	32	NR	NR	65.6	NR	No
	Initial ADA+MTX 12 weeks, then step-up therapy	week 52	33	NR	NR	63.6	NR	No
OPERA [97]	MTX + PBO + steroid	12 months	91	7	20	74	94	No
	ADA + MTX + steroid	12 months	89	7	11	82	93	No
GO-BEFORE	PBO + MTX	24 weeks	160	NR	NR	NR	61.3	Yes
	GOL + MTX	24 weeks	159	NR	NR	NR	73 [a]	Yes
GO-BEFORE [136]	PBO + MTX	52 weeks	160	NR	NR	NR	74.4	No
	GOL + MTX	52 weeks	159	NR	NR	NR	80.5	No

[a] = *P<0.05 reported*
[b] = *P<0.01 reported*
[c] = *p<0.01 analysed across all categories*

Population 2/3

There were three trials of head-to-head biologics for cDMARD experienced patients that reported EULAR response data (Table 15 EULAR Population 2/3 Head to head). ATTEST[66] showed that abatecept plus methotrexate and infliximab plus methotrexate responded similarly at six months follow-up. RED-SEA[104] reported adalimumab plus cDMARDs and etanercept 50mg once a week plus cDMARDs treated patients responding similarly well at one year follow-up. ADACTA[55] reported that significantly more tocilizumab plus placebo treated patients achieved a good EULAR response than adalimumab plus placebo treated patients at six months follow-up. ADACTA[55] and ATTEST[66] contributed EULAR data to the NMA, whereas RED-SEA[104] did not report data within 22-30 weeks follow-up.

Eleven other published trials reported EULAR data for biologics (Table 15 EULAR Population 2 vs DMARD(s) or placebo). With the exception of CTZ, data were available for all interventions of interest. Two adalimumab trials reported EULAR data. AUGUST II[68] reported a significantly better EULAR result for adalimumab plus methotrexate than for methotrexate plus placebo at six months. Adalimumab monotherapy had a significantly higher percentage of patients achieving at least moderate EULAR response than a placebo arm (van de Putte[112]). Of four etanercept trials, two compared etanercept monotherapy with etanercept combined with methotrexate. One of these studies (ADORE[56]) found similar EULAR responses for the groups at 16 weeks, whereas the other (JESMR [138]) reported significantly better results for combination therapy than for monotherapy at six months and one year. LARA[92] reported significantly better EULAR response for etanercept 50mg once a week plus methotrexate compared with methotrexate in combination with either sulfasalazine or hydrochloroqunine at six months. Etanercept plus methotrexate had a similar percentage of participants with good or moderate EULAR response to methotrexate plus DMARD (sulfasalazine, hydrochloroqunine or leflunomide) in the APPEAL[61] trial at 16 weeks follow-up. Golimumab plus methotrexate was significantly better than methotrexate plus placebo in terms of EULAR response at both 14 and 24 weeks follow-up in the GO-FORWARD[82] trial. Swefot[109] reported infliximab plus methotrexate having significantly better EULAR response than triple therapy with cDMARDS (sulfasalazine plus hydrochloroqunine plus methotrexate) at one year, with the difference between groups not significant at six months and two years. Tocilizumab monotherapy was investigated in two of the three tocilizumab trials reporting EULAR data. Tocilizumab monotherapy results were similar to Tocilizumab in combination with methotrexate, in the ACT-RAY[54] trial at six months. tocilizumab monotherapy treatment had significantly better EULAR responses at 12 weeks compared with placebo (Nishimoto 2004[96]). The TOWARD[111] trial reported significantly better EULAR responses for tocilizumab in combination with stable cDMARDS than for placebo in combination

with stable cDMARDS at six months. The following trials contributed EULAR data to the NMA: AUGUST II[68]; van de Putte 2004[112]; JESMR[138]; LARA[92]; GO-FORWARD[82]; Swefot[109]; ACT-RAY[54]; TOWARD[111]. ADORE[56] and APPEAL [61] did not have data within 22-30 weeks.

[redacted]

[a] = P<0.05 reported
[b] = P<0.01 reported

Table 15: EULAR: Population 2/3 biologic head to head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving no EULAR response	% achieving moderate EULAR response	% achieving good EULAR response	% EULAR responder (moderate/good)	In NMA?
ATTEST [66]	PBO+MTX	Day 197	102	45.1	44.1	10.8	54.9	Yes
	ABT + MTX	Day 197	150	23.3	56.7	20.0	76.7	Yes
	IFX + MTX	Day 197	156	34.0	42.9	23.1	66.0	Yes
RED-SEA[104]	ADA+cDMARDs	52weeks	60	40.4	33.3	26.3	59.6	No
	ETN50+cDMARDs	52weeks	60	51.5	16.7	31.7	48.4	No
ADACTA[55] [55]	TCZ + PBO	24 weeks	163	22.1	26.4	51.5 [b]	77.9	Yes
	ADA + PBO	24 weeks	162	45.1	35.1	19.8	54.9	Yes

Table 16: EULAR: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving no EULAR response	% achieving moderate EULAR response	% achieving good EULAR response	% EULAR responder (moderate/good)	In NMA?
AUGUST II[68]	MTX+PBO	26weeks	76	41	NR	NR	59	Yes
	ADA+MTX	26weeks	79	19	NR	NR	81 [a]	Yes
van de Putte 2004[112]	PBO	26 weeks	110	NR	NR	3.6	26.4	Yes
	ADAmon	26 weeks	113	NR	NR	8.8	55.8	Yes
ADORE[56,57]	ETNmon	16 weeks	156	NR	NR	NR	80.0	No
	ETN+MTX	16 weeks	151	NR	NR	NR	82.4%	No
JESMR	ETNmon	24 weeks	69	29.0	37.7	33.3	71.0	Yes
	ETN + MTX 6-8mg/week	24 weeks	73	4.1 [c]	43.8 [c]	52.1 [c]	95.9	Yes
JESMR	ETN mon	52 weeks	69	NR	NR	33.3	NR	No
	ETN + MTX 6-8mg/week	52 weeks	73	NR	NR	52.1 [b]	NR	No
LARA[92]	MTX+DMARD	24weeks	142	35.2	NR	12	64.8	Yes
	ETN50+MTX	24weeks	279	8.2	NR	47 [b]	91.8 [b]	Yes
APPEAL[61,141]	MTX plus DMARD (SSZ, HCQ or LEF)	16 weeks	103	NR	NR	NR	73.8	No
	ETN+MTX	16 weeks	197	NR	NR	NR	87.8	No
GO-FORWARD[82]	PBO + MTX	14 weeks	133	NR	NR	NR	44.4	No
	GOL + MTX	14 weeks	89	NR	NR	NR	70.8 [b]	No
GO-FORWARD	PBO + MTX	24 weeks	133	NR	NR	NR	42.1	Yes
	GOL + MTX	24 weeks	89	NR	NR	NR	71.9 [b]	Yes
Swefot[109]	SSZ + HCQ + MTX	23.8 weeks	130	NR	NR	23.8	NR	Yes
	IFX + MTX	23.8 weeks	128	NR	NR	33.6	NR	Yes
Swefot	SSZ + HCQ + MTX	12 months after study inclusion (8-9 months (35-39 weeks) after randomisation)	130	NR	NR	25	49	No
	IFX + MTX	12 months	128	NR	NR	39 [a]	60	No

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving no EULAR response	% achieving moderate EULAR response	% achieving good EULAR response	% EULAR responder (moderate/good)	In NMA?
		after study inclusion (8-9 months (35-39 weeks) after randomisation)						
Swefot	SSZ + HCQ + MTX	24 months after study inclusion (20-21 months (87-91 weeks) after randomisation)	130	NR	NR	31	50	No
	IFX + MTX	24 months after study inclusion (20-21 months (87-91 weeks) after randomisation)	128	NR	NR	38	59	No
ACT-RAY[54]	TCZ + PBO	24 weeks	276	NR	34.8	51.4	86.2	Yes
	TCZ + MTX	24 weeks	277	NR	27.8	61.7	89.5	Yes
Nishimoto 2004[96]	PBO	12 weeks	53	NR	NR	0	18.9	No
	TCZ mon	12 weeks	55	NR	NR	18.2 [b]	90.9 [b]	No
TOWARD[111]	PBO + stable cDMARDs	24 weeks	413	62.5	NR	NR	37.5	Yes
	TCZ + stable DMARDs	24 weeks	803	20.3	NR	NR	79.7 [b]	Yes
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DAS28

Population 1

Population 1 (methotrexate-naive patients) DAS

One head-to-head biologics trial of methotrexate-naive patients reported DAS28 data.[90] (Appendix 2, Table 355 DAS Population 1 Head to head trial). At 24 weeks follow-up, Kume [90] reported similar mean change from baseline in DAS28-ESR for adalimumab monotherapy and etanercept monotherapy.

Thirteen other trials reported DAS28 mean change or remission data for methotrexate-naive patient trials, comprising five adalimumab trials (GUEPARD[83], HIT HARD[84], OPERA [97], OPTIMA[98], PREMIER[99]), one etanercept trial (COMET[73]), one golimumab trial (GO-BEFORE), and five infliximab trials (ASPIRE [63], BeST[70] Durez 2007[76], IDEA [85], Quinn 2005 [100]). Across all interventions, where reported, mean DAS28 improved slightly in all treatment arms, including control cDMARD arms. Biologic treatment arms reported significantly higher percentage of patients meeting pre-defined DAS28 remission (usually <2.6), or having significantly more improved DAS28 than baseline, than controls for: adalimumab plus methotrexate than methotrexate plus placebo (HIT HARD[84], PREMIER[99]); adalimumab plus methotrexate plus steroid than methotrexate plus placebo than steroid (OPERA [97]); etanercept plus methotrexate than methotrexate plus placebo (COMET[73]); golimumab plus methotrexate than methotrexate plus placebo at six months (not one year follow-up) (GO-BEFORE); infliximab plus methotrexate than methotrexate plus placebo (ASPIRE, Quinn 2005 [100] 2005). Adalimumab monotherapy had similar DAS28 results to methotrexate plus placebo (PREMIER[99]), as did infliximab plus methotrexate to methotrexate plus MP (Durez 2007[76], IDEA). Step-up therapy with initial adalimumab (GUEPARD[83]) or infliximab (BeST) did not differ from control groups after one year or six months respectively. Results shown in table (Table 356 DAS Population 1 vs. DMARD(s) or PBO) in Appendix 2.

Population 2/3

Four head-to-head trials of cDMARD-experienced patients reported DAS28 results (ATTEST[66], AMPLE[60], RED-SEA[104], ADACTA[55]) (Appendix 2, Table 357 DAS Population 2 Head-to-head trials). Abatecept, adalimumab, etanercept 50mg once weekly, infliximab and tocilizumab treatment arms all showed some improvement in DAS28. There were similar levels of DAS28 improvement for abatecept plus methotrexate and infliximab plus methotrexate (both of which were significantly more improved than methotrexate plus placebo) (ATTEST[66]), abatecept and adalimumab monotherapies (AMPLE[60]), and adalimumab and etanercept 50mg once weekly both in combination with cDMARDs (RED-SEA[104]). ADACTA[55] reported significantly more improvement for tocilizumab monotherapy than for adalimumab monotherapy.

Twenty other trials reported DAS28 mean change or remission data for cDMARD experienced patient trials (Appendix 2, Table 358 DAS Population 2 vs DMARD(s) or PBO), comprising two abatecept trials (AIM[59], ASSET[64]), one adalimumab trial (van de Putte 2004[112]), two certolizumab pegol trials (CERTAIN[71], REALISTIC), five etanercept trials (CREATE IIB[86], JESMR, LARA[92], RACAT[101], APPEAL [61]), three golimumab trials (GO-FORTH[81], GO-FORWARD[82], Kay 2008[88]), two infliximab trials (START[108], Wong 2009[116]) and five tocilizumab trials (ACT-RAY[54], MEASURE[93], SAMURAI[105], SATORI[106], TOWARD[111]). Across all interventions, where reported, mean DAS28 improved in all treatment arms, including control cDMARD arms. Biologic treatments arms reported higher percentages of patients meeting pre-defined DAS28 remission (usually <2.6) than non-biologic control arms with one or two cDMARDs or baseline cDMARDs. There were significantly higher percentage of patients meeting pre-defined DAS28 remission (usually <2.6), or having significantly more improved DAS28 than baseline, than controls for: abatecept plus methotrexate than methotrexate plus placebo (AIM[59]); adalimumab monotherapy than placebo (van de Putte); etanercept 50mg once weekly plus methotrexate than methotrexate plus one other cDMARD (LARA[92], APPEAL [61]); etanercept 50mg once weekly plus methotrexate than methotrexate plus sulfasalazine plus hydrochloroqunine at 24 weeks (in an analysis of treatment completers only, although not after 48 weeks with option to switch therapy) (RACAT[101]); golimumab plus methotrexate than methotrexate plus placebo at six months (not one year follow-up) (GO-FORTH[81], GO-FORWARD[82], Kay 2008[88]); infliximab plus methotrexate than methotrexate plus placebo (START, Wong 2009[116]); tocilizumab plus methotrexate than tocilizumab monotherapy (ACT-RAY[54]) or than methotrexate plus placebo (MEASURE[93]); tocilizumab monotherapy than cDMARDs (SAMURAI[105]), although not compared with methotrexate plus placebo (SATORI[106]); tocilizumab plus DMARDS than DMARDs plus placebo (TOWARD[111]). Etanercept plus methotrexate performed significantly better than etanercept monotherapy (JESMR), although not at 16 weeks follow-up (ADORE[56]).

[redacted]

HAQ-DI

Population 1

Ten trials reported HAQ-DI change from baseline (Table 359 HAQ-DI Population 1 trials, Appendix 2). These comprised five adalimumab trials (GUEPARD[83], HIT HARD[84], OPERA,[97] OPTIMA[98], PREMIER[99]), two etanercept trials (COMET[73], ERA[77]), one golimumab trial (GO_BEFORE), and two infliximab trials (ASPIRE, BeST). There were improvements in HAQ-DI for most treatments,

interventions and controls, although there tended to be more improvement for biologics than control arms, although not in all cases (ERA[77]).

Population 2/3

Four head to head trials (ATTEST[66], AMPLE[60], ADACTA[55], DeFilippis 2006[75]) reported HAQ-DI change from baseline (Table 360 HAQ-DI Population 2 Head-to-head trials, Appendix 2). All trial arms improved HAQ-DI. Abatecept-treated patients achieved similar results to infliximab (ATTEST[66]) and adalimumab (AMPLE[60]). Tocilizumab monotherapy produced slightly more improvement than adalimumab monotherapy [significance testing not reported] (ADACTA[55]). In a small trial (n=32) etanercept plus methotrexate produced slightly better HAQ-DI results than infliximab plus methotrexate (DeFilippis 2006[75]).

Twenty seven other trials reported HAQ-DI change from baseline for cDMARD-experienced patients (Appendix 2, Table 361 HAQ-DI Population 2 vs. DMARD(s) or PBO), comprising two abatecept trials (AIM[59], ASSURE[65]), four adalimumab trials (CHANGE[72], DE019[74],van de Putte 2004[112], ARMADA[62]), two certolizumab pegol trials (CERTAIN[71], REALISTIC), ten etanercept trials (ADORE[56], etanercept Study 309[78], JESMR, Lan 2004, LARA[92], Moreland 1999[94], RACAT[101], Wajdula 2000[113], Weinblatt 1999[114], APPEAL [61]), two golimumab trials (GO-FORTH[81], GO-FORWARD[82]), four infliximab trials (ATTRACT[67], Durez 2004, START, Zhang 2006) and three tocilizumab trials (ACT-RAY[54], SATORI[106], TOWARD[111]). Generally, there was some improvement in HAQ-DI for all trial arms, with more improvement for biologics than control arms.

Joint counts and assessment of inflammation markers (CRP and ESR)

Population 1

The only head to head RCT in methotrexate-naïve patients identified in this review [90] did not report any follow-up or change data on joint counts or assessment of inflammation markers. A total of seven RCTs of biologic vs. DMARD(s) or PBO reported follow-up or change data on joint counts or assessment of inflammation markers in methotrexate-naïve patients (3 for adalimumab, 1 for etanercept, 1 for golimumab, and 2 for infliximab) (Table 362, Appendix 2). Statistically significant differences in swollen joint count favouring biologic treatment over comparator were reported for adalimumab (1 study) and etanercept (1 study). Statistically significant differences in tender joint count favouring biologic treatment over comparator were reported for adalimumab (2 studies) and golimumab (1 study). Statistically significant differences in CRP response favouring biologic treatment over comparator were reported for adalimumab (1 study). Statistically significant differences in ESR response were not identified in any trials.

Population 2/3

Four head to head RCTs reporting data on joint counts and/or assessment of inflammation markers in cDMARD-experienced patients were identified (Table 363, Appendix 2). Similar improvements were made in swollen joint count, tender joint count and CRP level among patients in the subcutaneous abatacept plus methotrexate and adalimumab plus methotrexate arms of the AMPLE trial.[142] Likewise, swollen joint count, tender joint count and CRP level were not significantly different between patients in the adalimumab plus cDMARDs and etanercept plus cDMARDs arms of the RED SEA trial.[104] The De Filippis trial[133] reported no difference in percentage change between arms for swollen joint count and CRP level but reported significantly greater improvements in tender joint count in the etanercept plus methotrexate arm relative to the infliximab vs. methotrexate arm. Finally, similar reductions in swollen joint count and tender joint count were reported for patients in the tocilizumab plus placebo adalimumab and adalimumab plus placebo tocilizumab arms in the double-dummy trial ADACTA.[55]

Twenty RCTs of biologic vs. DMARD(s) or PBO reported follow-up or change data on joint counts or assessment of inflammation markers in cDMARD-experienced patients (Table 364, Appendix 2). Statistically significant differences in swollen joint count favouring biologic treatment over comparator were reported in nine trials (1 adalimumab trial, 5 etanercept trials, 1 golimumab trial, 1 tocilizumab trial and [redacted]). Statistically significant differences in tender joint count favouring biologic treatment over comparator were reported in nine trials (1 adalimumab trial, 4 etanercept trials, 1 golimumab trials, 1 infliximab trial, 1 tocilizumab trial and [redacted]). Statistically significant differences in CRP response favouring biologic treatment over comparator were reported in six trials (1 adalimumab trial, 4 etanercept trials and 1 tocilizumab trial). Statistically significant differences in ESR response favouring biologic treatment over comparator were reported in seven trials (5 etanercept trials, 1 tocilizumab trial and [redacted]).

One trial of biologic and cDMARD combination therapy (etanercept plus methotrexate) versus biologic monotherapy (JESMR) reported significantly greater improvements in swollen joint count tender joint count and ESR in the combination therapy arm, but significantly greater improvements in CRP in the monotherapy arm.[87] Another trial of biologic and cDMARD combination therapy versus monotherapy (ACT-RAY; tocilizumab plus methotrexate versus tocilizumab plus placebo) reported similar changes from baseline in swollen joint count and tender joint count.[54]

Patient and physician global assessments of disease activity

Population 1

No data were available for this outcome from the single identified head to head RCT in methotrexate-naïve patients. [90] Four population 1 trials in methotrexate-naïve patients contributed global assessment evidence (presented in Table 365), of which 2 were for adalimumab, 1 for golimumab and 1 for infliximab. Of these 4 trials, statistically significant improvements in global assessments of disease activity were reported for 1 trial favouring golimumab plus methotrexate over placebo and methotrexate (GO-BEFORE),[80] and for 1 trial (BeST)[143] which favoured initial combination cDMARD therapy plus prednisone and initial combination cDMARD therapy plus infliximab over sequential cDMARD monotherapy and step-up combination cDMARD therapy.

Population 2/3

Patient and physical global assessment of disease activity data were reported in 3 head to head RCTs of cDMARD-experienced patients (Table 366). No statistically significant differences in treatment response were reported.

A total of 23 further RCTs evaluated global assessments of disease activity in 4 adalimumab trials, 4 etanercept trials, 1 golimumab trial and 3 infliximab trials, Table 367.

5.2.3.2 Radiological progression / Joint damage

Population 1

Data were extracted from RCTs where absolute baseline and follow-up, mean change from baseline or proportion change from baseline in joint outcomes were available.

No joint damage / radiological progression data were identified from the single identified head-to-head population 1 trial.[90] Six trials of biologic interventions vs. DMARD(s) or PBO in methotrexate-naïve patients reported change in radiographic scores and/or radiographic non-progression (3 adalimumab trials, 2 etanercept trials and 1 infliximab trial). Joint outcomes were assessed using a range of radiographic scores,[144] and magnetic resonance imaging. Data for radiographic scores are presented in Table 368 (Appendix 2). Statistically significant results favouring intervention in the reduction of radiological progression were reported for 2 adalimumab trials, 1 etanercept trial, and 1 infliximab trial. Two trials (1 each for adalimumab and golimumab) provided joint assessment data as measured by magnetic resonance imaging (both of which reported statistically significant findings favouring biologic treatment (Table 369).

Population 2/3

One head to head trial (Table 370) (adalimumab vs. abatacept) and ten trials of biologic interventions vs. DMARD(s) or PBO in cDMARD-experienced patients reported change in radiographic scores and/or rates of radiographic non-progression (1 for abatacept, 1 for adalimumab, 3 for etanercept, 1

for golimumab, 2 for infliximab and 2 for tocilizumab) (Table 371). Statistically significant results indicating reduced radiological progression were reported for 1 abatacept trial, 1 adalimumab trial, 2 etanercept trials, 1 golimumab trial, both infliximab trials, and 1 tocilizumab trial. Joint outcome data as assessed by magnetic resonance imaging were presented in 3 trials (1 each for abatacept, golimumab and infliximab) (Table 372), with statistically significant benefits to joint outcomes reported for the golimumab trial.

5.2.3.3 Pain

Population 1

Six trials reported pain VAS score change from baseline (Table 373 Pain VAS Population 1 vs DMARD(s) or PBO, Appendix 2). These comprised three adalimumab trials (OPERA [97], OPTIMA[98], PREMIER[99]), one etanercept trial (COMET[73]), one golimumab trial (GO-BEFORE), and one infliximab trial (BeST). There were reductions in pain VAS for most treatments, and there were significant benefits for all four biologics compared with controls.

Population 2/3

Two head-to-head trials (AMPLE[60], DeFilippis 2006[75]) reported pain VAS change from baseline (Table 374 Pain VAS Population 2 Head to head trials, Appendix 2). All trial arms reduced pain VAS score. No significant differences were reported between groups.

Twenty seven other trials reported Pain VAS change from baseline for cDMARD-experienced patients (Appendix 2, Table 375 HAQ-DI Population 2 vs DMARD(s) or PBO), comprising two abatecept (AIM[59], ASSURE[65]), five adalimumab trials (CHANGE[72], DE019[74],van de Putte 2004[112], ARMADA[62], Kim 2007), one certolizumab pegol trial (CERTAIN[71]), nine etanercept trials (ADORE[56], etanercept Study 309[78], JESMR, Lan 2004, LARA[92], Moreland 1999[94], RACAT[101], Weinblatt 1999[114], APPEAL[61]), one golimumab trial (GO-FORWARD[82]), two infliximab trials (ATTRACT[67], START) and one tocilizumab trial (ACT-RAY[54]). Generally, there was some reduction in pain VAS for all trial arms. Abatecept had similar reductions compared with control groups (AIM[59], ASSURE[65]). There was at least one trial reporting significantly more pain VAS reduction than control for each of adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. In the RACAT[101] trial etanercept 50mg once weekly plus methotrexate had similar results to methotrexate plus sulfasalazine plus hydrochloroquinine. In the ACT-RAY[54] trial tocilizumab monotherapy had similar results to tocilizumab plus methotrexate.

5.2.3.4 Fatigue

Population 1

The only head to head RCT in MTX-naïve patients identified in this review [90] did not report any follow-up or change data on fatigue. A total of 3 RCTs of biologic vs. DMARD(s) or PBO reported follow-up or change data on fatigue in MTX-naïve patients (2 for adalimumab and 1 for etanercept) (Tables 376 – 377, Appendix 2). Statistically significant differences favouring biologic treatment over comparator were reported for VAS score (1 etanercept trial) and FACIT-F score (1 adalimumab trial). One further adalimumab trial reported significant differences between adalimumab and methotrexate arms at follow-up in a mixed-model repeated measures analysis, but the values appear to be similar.

Population 2/3

Two head to head RCTs reporting data on fatigue in cDMARD-experienced patients were identified (Tables 378 - 379, Appendix 2). Similar improvements were made on fatigue VAS score among patients in the subcutaneous abatacept plus methotrexate and adalimumab plus methotrexate arms of the AMPLE trial [142] and on FACIT-F score among patients in the tocilizumab plus placebo adalimumab and adalimumab plus placebo tocilizumab arms in the ADACTA trial.[55]

Twenty RCTs of biologic vs. DMARD(s) or PBO reported follow-up or change data on fatigue data in cDMARD-experienced patients (Tables 380 - 381, Appendix 2). A statistically significant difference in VAS fatigue score swollen joint count favouring biologic treatment over comparator was reported in one abatacept trial. Statistically significant differences in FACIT-F score favouring biologic treatment over comparator were reported in four trials (1 adalimumab trial, 1 etanercept trial, 1 golimumab trial, and 1 tocilizumab trial). Mean (SD) change from baseline in the Fatigue Assessment Scale has been reported for the CERTAIN trial of 0.1 (2.12) in the placebo arm and -1.2 (2.24) in the CTZ arm at week 24 (clinicaltrials.gov, NCT00674362) and [redacted].[145]

5.2.3.5 Health-related quality of life

Population 1

The only head to head RCT in MTX-naïve patients identified in this review [90] did not report any follow-up or change data on health-related quality of life. A total of 9 RCTs of biologic vs. DMARD(s) or PBO reported follow-up or change data on health-related quality of life in MTX-naïve patients (4 for adalimumab, 2 for etanercept and 3 for infliximab) (Tables 382 - 387, Appendix 2). Statistically significant differences in SF-36 components and domains favouring biologic treatment over comparator were reported for adalimumab (1 study), etanercept (2 studies) and infliximab (1 study). One further adalimumab trial reported significant differences between adalimumab and methotrexate arms at follow-up in a mixed-model repeated measures analysis, but the values appear to be similar. One study reported a statistically significant difference on the SF-12 physical component

score for adalimumab. Statistically significant differences in RAQoL score favouring biologic treatment over comparator were reported for adalimumab (1 study) and infliximab (1 study). One further adalimumab trial reported significant differences on SF6D score between adalimumab and methotrexate arms at follow-up in a mixed-model repeated measures analysis, but the values appear similar. One study reported a statistically significant difference on EQ5D score for adalimumab.

Population 2/3

Three head to head RCTs reporting data on health-related quality of life in cDMARD-experienced patients were identified (Tables 388 – 390, Appendix 2). Similar improvements were made on SF-36 components and domains scores among patients in the subcutaneous abatacept plus methotrexate and adalimumab plus methotrexate arms of the AMPLE trial[142] and among patients in the abatacept plus methotrexate, infliximab plus methotrexate and methotrexate plus placebo arms of the ATTEST trial.[66] Significantly greater improvements were reported on SF-36 mental component score among patients in the tocilizumumab (plus placebo adalimumab) arm than in the adalimumab (plus placebo tocilizumab) arm in the ADACTA trial.[55] Similar improvements were made on EQ-5D score among patients in the adalimumab and etanercept arms of the RED-SEA trial.[104]

Nine RCTs of biologic vs. DMARD(s) or PBO reported follow-up or change data on health-related quality of life data in cDMARD-experienced patients (Tables 391 - 396, Appendix 2). Statistically significant differences in SF-36 components and domains scores favouring biologic treatment over comparator were reported in 5 trials (1 abatacept trial, 1 etanercept trial, 1 golimumab trial, 1 infliximab trial and 1 tocilizumab trial). [redacted]. Statistically significant differences in EQ-5D domain scores favouring biologic treatment over comparator were reported in 1 etanercept trial and a further etanercept trial reported a statistically significant improvement in EuroQol VAS score.

5.2.3.6 Extra-articular manifestations of disease

No included RCTs specifically evaluated the impact of biologic interventions on extra-articular manifestations of RA.

5.2.3.7 Adverse effects of treatment

Data were extracted relating to discontinuations due to adverse events, number of patients experiencing 1 or more adverse events and number of patients experiencing 1 or more serious adverse event. Details are presented in Tables 397 – 399. Specific adverse events of important note as highlighted in the FDA prescribing information for each intervention were extracted from RCTs and

associated LTEs of individual included RCTs and tabulated (Tables 400 to 402, Appendix 2). These key safety issues identified across the range of interventions included the number of patients experiencing one or more infections, number of patients experiencing one or more serious infections (with pneumonia and reactivation of tuberculosis noted as important safety issues), number of patients experiencing one or more malignancy, and the occurrences of infusion-related or injection-site reactions (as appropriate to the mode of administration for each intervention).

5.2.3.8 Mortality

Details of number of deaths, cause(s) of death and judgement by study team / adjudicator as to whether death was potentially attributable to study drug were extracted and have been tabulated (Tables 403 to 402, Appendix 2).

5.2.4 Additional evidence (trial data not eligible for full systematic review but included to inform MTC sensitivity analyses for populations 2 and 3)

Study and population characteristics for the trials ineligible for the full systematic review but provided as additional evidence to inform sensitivity analyses are presented in Table 342) (Appendix 2). Two RCTs in which tofacitinib was evaluated were included as evidence to supplement the network.

Table 17: ACR response: population 2/3 RCTs used in the sensitivity analyses of the NMA

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
ACQUIRE	ABT s.c. +PBO + MTX	26 weeks	736	74.8	50.2	25.8	Y (SAs)
	ABT i.v..+ PBO +MTX	26 weeks	721	74.3	48.6	24.2	
NCT00254293	PBO + MTX	25.7 weeks	119	35.3	11.8	1.7	Y (SAs)
	ABT i.v..+ MTX	25.7 weeks	115	60 [a]	36.5 [a]	16.5 [a]	
ORAL STANDARD	PBO + MTX	26 weeks	106	28.3	12	2	Y (SAs)
	TOF5 + MTX	26 weeks	196	51.5	36	20	
	TOF10 + MTX	26 weeks	196	52.6	33	22.5	
	ADA + MTX	26 weeks	199	47.2	27	9.5	
Yamamoto 2011 / JRAPID	PBO + MTX	24 weeks	77	24.7	16.9	1.3	Y (SAs)
	CTZ + MTX	24 weeks	82	73.2 [b]	54.9 [b]	29.3 [b]	
RA0025	PBO + MTX	24 weeks	40	27.5	20	2.5	Y (SAs)
	CTZ + MTX	24 weeks	81	66.7 [b]	43.2 [a]	17.3 [a]	
RAPID1	PBO + MTX	24 weeks	198	13.6	7.6	3	Y (SAs)
	CTZ + MTX	24 weeks	388	58.8 [b]	37.1 [b]	21.4 [b]	
RAPID2	PBO + MTX	24 weeks	127	8.7	3.1	0.8	Y (SAs)
	CTZ + MTX	24 weeks	246	57.3 [b]	32.5 [b]	15.9 [a] (comparison of ORs from logistic regressions)	
TEAR	MTX mon	24 weeks	379	39.39	19	3.43	Y (SAs)
	MTX + SSZ + HCQ	24 weeks	132	55.32	31.14	8.52	
	ETN50 + MTX	24 weeks	244	55.7	32.3	12.04	
TEMPO	MTX mon	24 weeks	228	74.18	41.31	15.9	Y (SAs)
	ETN mon	24 weeks	223	71.58	41.31	17.98	
	ETN + MTX	24 weeks	231	82.53	60.09	36.65	
LITHE [146]	PBO + MTX	24 weeks	393	27	10	2	Y (SAs)
	TCZ + MTX	24 weeks	398	56 [b]	32 [b]	13 [b]	
OPTION	PBO + MTX	24 weeks	204	26	11	2	Y (SAs)
	TCZ + MTX	24 weeks	205	59 [b]	44 [b]	22 [b]	
AMBITION [122]	MTX	24 weeks	259	47.7	30.7	15.9	Y (SAs)
	TCZ	24 weeks	265	71.9 [a]	40.4	28.1	
van der Heijde 2013	PBO + MTX	26 weeks	160	25.3	8.4	1.3	Y (SAs)

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving ACR20 response	% achieving ACR50 response	% achieving ACR70 response	Data used in NMA?
[119]	TOF5 + MTX	26 weeks	321	51.5 [b added vs PBO+MTX]	32.4 [b added vs PBO+MTX]	14.6 [b added vs PBO+MTX]	
	TOF10 + MTX	26 weeks	316	61.8 [b added vs PBO+MTX]	43.7 [b added vs PBO+MTX]	22.3 [b added vs PBO+MTX]	
Kremer 2012 [118]	PBO + MTX	24 weeks	69	24.62	23.08	19.87	Y (SAs)
	TOF5 + MTX	24 weeks	71	47.44	33.33	19.23 [a added vs PBO+MTX]	
	TOF10 + MTX	24 weeks	74	54.49 [a added vs PBO+MTX]	34.62	16.67 [a added vs PBO+MTX]	

Table 18: EULAR response: population 2/3 RCTs used in the sensitivity analyses of the NMA

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	% achieving no EULAR response	% achieving moderate EULAR response	% achieving good EULAR response	% EULAR responder (moderate/good)	In NMA?
JRAPID[123]	PBO + MTX	24 weeks	77	70.1	NR	NR	29.9	Y (SAs)
Yamamoto 2011 / JRAPID	CTZ + MTX	24 weeks	82	14.6	NR	NR	85.4	Y (SAs)
RAPID1[129]	PBO + MTX	24 weeks	199	72.9	NR	NR	[redacted]	Y (SAs)
RAPID1 [redacted]	CTZ + MTX	24 weeks	393	19.1	NR	NR	[redacted]	Y (SAs)
AMBITION[121,121]	MTX	24 weeks	259	35.1	49.8	15.1	64.9	Y (SAs)
AMBITION	TCZ mon	24 weeks	265	17.7	44.5	37.7	82.3	Y (SAs)
OPTION[126]	PBO+MTX	24 weeks	205	64.9	32.2	2.9	28.8	Y (SAs)
OPTION	TCZ+ MTX	24 weeks	204	20.6	41.2 [b]	38.2 [b]	79.4	Y (SAs)

5.3 NMA Results

For ease of interpretation a summary of the data used in the NMA is provided. These are contained in Table 19 through to Table 22. As described earlier a number of sensitivity analyses were undertaken to allow the impact of further information, albeit subject to potential biases, including a small proportion of patients with prior bDMARD use, and including studies in which the patients (for populations 2 and 3) have low background methotrexate use and may not be truly methotrexate failures. The RCTs have been grouped into those that fit within the Assessment Group base case, and those that have prior bDMARD use and / or low background methotrexate use.

Additionally the trials with EULAR data have been further subdivided into whether data were reported for all three categories or whether these were aggregated differently, for example only values for response or no response was provided. Data from the TACIT study was provided as academic-in-confidence.

Tables 19 and 20 provide data for populations 2 and 3 using EULAR and ACR criteria respectively.

Tables 21 and 22 provide data for population 1 using EULAR and ACR criteria respectively. Only one RCT that reported EULAR data met the criteria for inclusion.

In all tables the data have been apportioned so that these are mutually exclusive, i.e. that ACR20 now refers to patients who made an ACR 20 response but not an ACR50 response. Typically the RCTs would include patients with an ACR50 or ACR70 response within the ACR20 category, with the sum of the ACR responses being larger than the total number within the trial arm.

Table 19: The EULAR data used in the MTC for populations 2 and 3

	Interventions			Mean Disease Duration	Intervention 1				Intervention 2				Intervention 3			
	1	2	3	Weeks	n No Response	Mod EULAR	Good EULAR	N Tot Pop	n No Response	Mod EULAR	Good EULAR	N Tot Pop	n No Response	Mod EULAR	Good EULAR	N Tot Pop
Base case – full data reported																
ACT-RAY	TCZ+	TCZ		676	29	77	171	277	38	96	142	276				
ADACTA	ADA	TCZ		354	73	57	32	162	36	43	84	163				
ATTEST	cDMARD	ABT iv+	IFX +	405	46	45	11	102	35	85	30	150	53	67	36	156
JESMR	ETN+	ETN		485	3	32	38	73	20	26	23	69				
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
van de Putte	ADA	PBO		577	50	53	10	113	81	25	4	110				
Base case - No Response and Response (i.e. Moderate and Good combined) reported																
AUGUST II	cDMARD	ADA+		447	31			76	15			79				
GO-FORWARD	cDMARD	GOL+		421	77			133	25			89				
LARA	Int CDMARD	ETN+		430	50			142	23			279				
TOWARD	cDMARD	TCZ+		510	258			413	163			803				
Base case - Good and Not Good (i.e. Moderate and No Response combined) reported																
Swefot	Int CDMARD	IFX+		27			31	130			43	128				
Sensitivity Analyses: Prior bDMARD use for some patients – full data reported																
OPTION	cDMARD	TCZ+		398	133	66	6	205	42	84	78	204				
Sensitivity Analyses: Prior biologics - No Response and Response (i.e. Moderate and Good combined) reported																

RAPID1	cDMARD	CTZ+		319	145	54		199	75	318		393				
Yamamoto	cDMARD	CTZ+		296	54	23		77	12	70		82				
Sensitivity Analyses: Prior biologics – full data reported and low background methotrexate use																
AMBITION	cDMARD	TCZ		330	91	129	39	259	47	118	100	265				

ABT iv – abatacept iv; ADA – adalimumab; bDMARD – biologic DMARD; Bios – a clinician's choice of adalimumab or etanercept or infliximab all with methotrexate; cDMARD – conventional DMARDs; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; Int cDMARD – Intensive cDMARDs; PBO – placebo; TCZ – tocilizumab;

A '+' indicates the intervention was in combination with methotrexate

Table 20: The ACR data used in the MTC for populations 2 and 3

	Interventions				Mean Disease Duration	Intervention 1					Intervention 2				
Trial Name	1	2	3	4	Weeks	n No Response	n ACR20 Response	nACR50 response	nACR70 response	N Tot Pop	n No Response	n ACR20 Response	nACR50 response	nACR70 response	N Tot Pop
Base case – full data reported															
IIbCREATE	cDMARD	ETN+			419	44	10	8	3	65	22	12	15	15	64
ACT-RAY	TCZ+	TCZ			676	79	72	58	68	277	82	83	41	70	276
ADACTA	ADA	TCZ			354	82	35	16	29	162	57	29	24	53	163
AIM	cDMARD	ABT iv+			449	132	50	23	14	219	139	121	87	86	433
AMPLE	ADA+	ABT sc+			94	117	72	65	74	328	108	65	68	77	318
ARMADA	cDMARD	ADA+			607	53	4	2	3	62	22	8	19	18	67
ATTEST	cDMARD	ABT iv+	IFX+		405	64	24	12	10	110	52	41	31	32	156
ATTRACT	cDMARD	IFX+			N/R	65	15	4	0	84	38	22	16	7	83
AUGUST II	cDMARD	ADA+			447	40	24	8	4	76	23	26	16	14	79
Certain	cDMARD	CTZ+			239	82	8	5	3	98	61	15	11	9	96
CHANGE	ADA	PBO			477	51	18	11	11	91	75	7	4	1	87
De Filippis	ETN+	IFX+				7	5	3	1	16	7	4	4	1	16
DE019	cDMARD	ADA+			569	141	40	14	5	200	76	50	38	43	207
ETN309	cDMARD	ETN+	ETN		341	36	7	6	1	50	27	22	27	25	101
GO-FORTH	cDMARD	GOL+			455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD	cDMARD	GOL+			421	96	19	11	7	133	36	20	15	18	89
JESMR	ETN+	ETN			485	7	19	19	28	73	25	11	15	18	69

	Interventions				Mean Disease Duration	Intervention 1					Intervention 2				
Trial Name	**1**	**2**	**3**	**4**	**Weeks**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
Kim2007	cDMARD	ADA+			356	40	14	4	5	63	25	12	14	14	65
LARA	Int cDMARD	ETN+			430	71	38	17	16	142	47	59	76	97	279
Mathias	ETN	PBO			598	31	15	20	12	78	71	5	3	1	80
O'Dell	Int cDMARD	ETN+			271	70	48	33	8	159	73	32	32	26	163
SAMURAI	cDMARD	TCZ			119	89	30	16	10	145	28	39	37	53	157
SATORI	cDMARD	TCZ			447	48	5	4	7	64	12	16	13	20	61
STAR	cDMARD	ADA+			541	207	75	25	11	318	150	76	45	47	318
START	cDMARD	IFX			N/R	271	57	18	17	363	152	93	65	50	360
TOWARD	cDMARD	TCZ			510	312	64	25	12	413	315	186	137	165	803
van de Putte	ADA	PBO			577	61	27	11	14	113	89	12	7	2	110
Weinblatt	cDMARD	ETN+			676	22	7	1	0	30	17	19	14	9	59
Sensitivity Analyses: Prior bDMARD use for some patients – full data reported															
ACQUIRE	ABT iv+	ABT sc+			398	186	185	176	174	721	185	181	180	190	736
Kremer	cDMARD	TOF5+	TOF10+		444	52	1	2	14	69	37	10	10	14	71
LITHE	cDMARD	TCZ+			476	287	67	31	8	393	174	96	76	52	398
NCT00254293	cDMARD	ABT iv			483	77	28	12	2	119	46	27	23	19	115
OPTION	cDMARD	TCZ+			398	151	31	18	4	204	84	31	45	45	205
RA0025	cDMARD	CTZ+			303	29	3	7	1	40	27	19	21	14	81
RAPID1	cDMARD	CTZ+			319	171	12	9	6	198	160	84	61	83	388

	Interventions				Mean Disease Duration	Intervention 1					Intervention 2				
Trial Name	**1**	**2**	**3**	**4**	**Weeks**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
RAPID2	cDMARD	CTZ+			308	116	7	3	1	127	105	61	41	39	246
van der Heijde	cDMARD	TOF5+	TOF10+		467	120	27	11	2	160	156	61	57	47	321
Yamamoto	cDMARD	CTZ+			296	58	6	12	1	77	22	15	21	24	82
Sensitivity Analyses: Prior biologics.- No ACR50 or ACR70 reported.															
ORAL STANDARD	cDMARD	ADA+	TOF5+	TOF10+	402	76	30			106	105	94	n/a	n/a	199
Sensitivity Analyses: Prior biologics – full data reported, and low background methotrexate use															
AMBITION	cDMARD	TCZ			330	46	15	13	14	88	25	28	11	25	89
Sensitivity analyses: low background methotrexate use															
TEAR	cDMARD	Int cDMARD	ETN+		18	230	77	59	13	379	59	32	30	11	132
TEMPO	cDMARD	ETN+	ETN		345	59	75	58	36	228	40	52	54	85	231

	Intervention		Intervention 3					Intervention 4				
Trial Name	**3**	**4**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
Base case – full data reported												
ATTEST	IFX+		67	37	21	40	165					
ETN309	ETN		27	28	26	22	103					

	Intervention		Intervention 3					Intervention 4				
Trial Name	**3**	**4**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
Sensitivity Analyses: Prior bDMARD use for some patients – full data reported												
Kremer	TOF10		34	15	13	12	74					
van der Heijde	TOF10		121	57	68	70	316					
Sensitivity Analyses: Prior biologics.- No ACR50 or ACR70 reported.												
ORAL STANDARD	TOF5	TOF10	95	101	n/a	n/a	196	93	103	n/a	n/a	196
Sensitivity analyses: low background methotrexate use												
TEAR	ETN+		109	57	49	29	244					
TEMPO	ETN		63	68	52	40	223					

ABT iv – abatacept iv; ABT sc – abatacept sc; ADA – adalimumab; bDMARD – biologic DMARD; Bios – a clinician's choice of adalimumab or etanercept or infliximab all with methotrexate; cDMARD – conventional DMARDs; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; Int cDMARD – Intensive cDMARDs; NR – Not Reproted; PBO – placebo; TCZ – tocilizumab; TOF5 – tofacitinib 5mg; TOF10 – tofacitinib 10mg

A '+' indicates the intervention was in combination with methotrexate

Table 21: The EULAR data for population 1

	Interventions			Mean Disease Duration	Intervention 1				Intervention 2			
	1	2	3	Weeks	n No Response	Mod EULAR	Good EULAR	N Tot Pop	n No Response	Mod EULAR	Good EULAR	N Tot Pop
Base case - No Response and Response (i.e. Moderate and Good combined) reported												
Go-BEFORE	cDMARD	GOL+		166	62			160	43			159

cDMARD – conventional DMARDs; GOL – golimumab; IFX – infliximab;

A '+' indicates the intervention was in combination with methotrexate

Table 22: The ACR data used in the MTC for population 1

	Interventions				Mean Disease Duration	Intervention 1					Intervention 2				
Trial Name	**1**	**2**	**3**	**4**	**Weeks**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
Base case – full data reported															
HIT HARD	cDMARD	ADA+			7	27	16	19	23	85	20	13	13	41	87
OPTIMA	cDMARD	ADA+			18	222	119	88	88	517	153	93	88	181	515
ERA	cDMARD	ETN			52	90	58	38	31	217	65	55	42	45	207
Durez	cDMARD	IFX+			21	10	3	1	0	14	2	3	5	5	15
Go-BEFORE	cDMARD	GOL+			166	81	32	22	25	160	61	34	26	38	159
PREMIER	cDMARD	ADA+	ADA		38	99	54	47	57	257	84	27	43	114	268
Base case –data reported only for ACR20 and ACR70 (20 patients had an ACR 70 response in Intervention 1 and 39 in Intervention 2)															
BeST	cDMARD	IFX+	Int CDMARD	Step Up Int cDMARD	NR	63	43			126	33	56			128

	Intervention		Intervention 3					Intervention 4				
Trial Name	**3**	**4**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
Base case – full data reported												
PREMIER	ADA		128	50	42	54	274					
Base case –data reported only for ACR20 and ACR70 (33 patients had an ACR 70 response in Intervention 3 and 15 in Intervention 4)												
BeST	Int CDMARD	Step Up Int	39	61			133	48	58			121

	Intervention		Intervention 3					Intervention 4				
Trial Name	**3**	**4**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**	**n No Response**	**n ACR20 Response**	**nACR50 response**	**nACR70 response**	**N Tot Pop**
		cDMARD										

ADA – adalimumab; cDMARD – conventional DMARDs; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; Int cDMARD – Intensive cDMARDs; Step Up Int cDMARD – Int cdMARD with escalation of doses as required.

A '+' indicates the intervention was in combination with methotrexate

5.3.1 Population 1 (MTX-naïve)

5.3.1.1 ACR

A network meta-analysis was used to compare the effects of adalimimub (with and without MTX), etanercept, infliximab + MTX, golimumab + MTX, Intensive cDMARDs plus prednisolone, and step-up combination cDMARDs relative to cDMARDs on ACR response.

Data were available from 7 studies comparing two, three or four interventions.

Figure 4 presents the network of evidence and Table 23 presents the frequency with which each pair of treatments was compared. There are seven treatment effects to estimate from seven studies.

Figure 4: ACR – Network of evidence

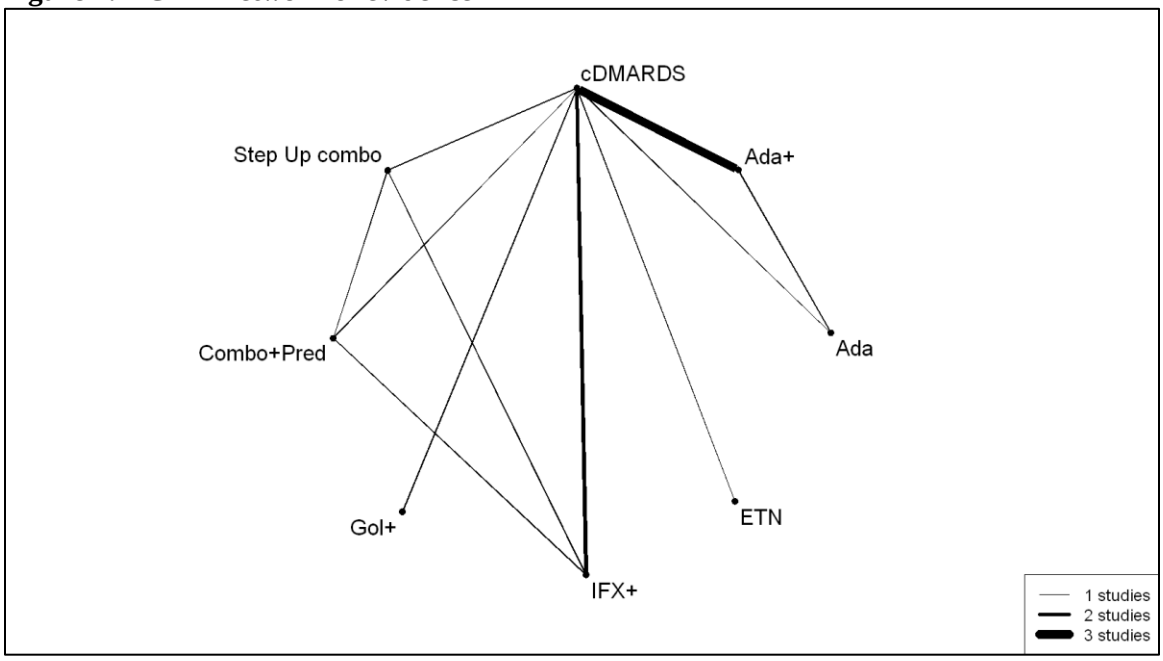


Table 23: ACR – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ADA+	ADA	ETN	IFX+	Gol+	Combo+Pred	Step-up Combo
cDMARDs	-	3	1	1	2	1	1	1
ADA+ MTX	-	-	1					
ADA	-	-	-					
ETN	-	-	-	-				
IFX+ MTX	-	-	-	-	-		1	1
Gol+ MTX	-	-	-	-	-	-		
Intensive cDMARDs +prednisolone	-	-	-	-	-	-	-	1
Step-up combination cDMARDs	-	-	-	-	-	-	-	-

Table 24 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 25 presents the probabilities of treatment rankings.

There was some suggestion that model was not a good fit to all of the data, with the total residual deviance, 59.23, being larger than would be expected given the total number of data points, 47, included in the analysis. The largest residual deviance, 18.76 (compared with 9 data points), was from the PREMIER study.

The between-study standard deviation was estimated to be 0.16 (95% CrI: 0.00, 0.52), which implies mild to moderate heterogeneity between studies in intervention effects.

All interventions except for adalimumab were associated with beneficial treatment effects relative to cDMARDs with the greatest effect being associated with infliximab + MTX. However, the treatment effects were only statistically significant for adalimumab + MTX, infliximab + MTX and Intensive cDMARDs +prednisolone at a conventional 5% level. infliximab + MTX (probability of being the best 0.785) was the treatment that was most likely to be the most effective interventions.

Table 24: ACR – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ADA+MTX	-0.4239	0.1378	-0.4257	-0.6999, -0.1367
ADA	0.1429	0.2113	0.1402	-0.2974, 0.5921
ETN	-0.2722	0.2337	-0.2686	-0.7704, 0.2075
IFX+MTX	-0.7761	0.2382	-0.7501	-1.3440, -0.3816
Gol+MTX	-0.3059	0.2447	-0.3079	-0.7986, 0.1966
Intensive cDMARDs +prednisolone	-0.5501	0.2468	-0.5362	-1.1070, -0.0968
Step-up combination cDMARDs	-0.2133	0.2526	-0.2006	-0.7798, 0.2437
Between study SD	0.1564	0.1415	0.1154	0.0032, 0.5230

Table 25: ACR – Probability of treatment rankings

	Rank							
Intervention	1	2	3	4	5	6	7	8
cDMARDs	0.000	0.000	0.001	0.005	0.031	0.198	0.657	0.108
ADA+ MTX	0.036	0.187	0.388	0.243	0.105	0.035	0.005	0.002
ADA	0.001	0.001	0.006	0.012	0.028	0.058	0.130	0.762
ETN	0.023	0.060	0.117	0.217	0.287	0.214	0.050	0.032
IFX+MTX	0.785	0.152	0.040	0.018	0.005	0.001	0.000	0.000
Gol+ MTX	0.035	0.083	0.158	0.240	0.248	0.159	0.046	0.031
Intensive cDMARDs +prednisolone	0.115	0.490	0.190	0.117	0.064	0.015	0.006	0.003
Step-up combination cDMARDs	0.005	0.027	0.101	0.149	0.231	0.320	0.105	0.062

Table 26, 27 and 28 presents the probabilities of achieving at least an ARC20 response, at least an ACR50 response and at least an ACR70 response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 26: ACR – Probability of achieving at least an ACR20 response

	Mean	SD	Median	95% CrI
cDMARDs	0.5608	0.0348	0.5608	0.4926, 0.6292
ADA+ MTX	0.7157	0.0544	0.7180	0.5991, 0.8146
ADA	0.5042	0.0863	0.5046	0.3216, 0.6807
ETN	0.6604	0.0867	0.6638	0.4691, 0.8260
IFX+MTX	0.8163	0.0617	0.8183	0.6890, 0.9359
Gol+ MTX	0.6720	0.0895	0.6769	0.4717, 0.8342
Intensive cDMARDs +prednisolone	0.7520	0.0773	0.7547	0.5879, 0.8995
Step-up combination cDMARDs	0.6382	0.0929	0.6392	0.4515, 0.8282

Table 27: ACR – Probability of achieving at least an ACR50 response

	Mean	SD	Median	95% CrI
cDMARDs	0.3141	0.0465	0.3123	0.2273, 0.4109
ADA+ MTX	0.4747	0.0738	0.4744	0.3287, 0.6223
ADA	0.2699	0.0792	0.2647	0.1282, 0.4460
ETN	0.4171	0.0989	0.4130	0.2263, 0.6285
IFX+MTX	0.6088	0.0976	0.6064	0.4229, 0.8133
Gol+ MTX	0.4301	0.1030	0.4276	0.2275, 0.6439
Intensive cDMARDs +prednisolone	0.5232	0.1048	0.5203	0.3226, 0.7446
Step-up combination cDMARDs	0.3950	0.1045	0.3878	0.2096, 0.6265

Table 28: ACR – Probability of achieving at least an ACR70 response

	Mean	SD	Median	95% CrI
cDMARDs	0.1696	0.0351	0.1677	0.1064, 0.2445
ADA+ MTX	0.2977	0.0664	0.2950	0.1751, 0.4369
ADA	0.1412	0.0565	0.1345	0.0520, 0.2717
ETN	0.2517	0.0840	0.2443	0.1081, 0.4416
IFX+MTX	0.4271	0.1035	0.4187	0.2486, 0.6648
Gol+ MTX	0.2627	0.0882	0.2554	0.1090, 0.4574
Intensive cDMARDs +prednisolone	0.3444	0.1005	0.3352	0.1724, 0.5742
Step-up combination cDMARDs	0.2345	0.0876	0.2235	0.0984, 0.4413

5.3.2 Populations 2/3 (MTX-experienced populations)

5.3.2.1 EULAR – Main Trials

A network meta-analysis was used to compare the effects of abatacept iv + MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo (PBO), tocilizumab (with and without MTX) and the grouped biologics from TACIT RCT, relative to cDMARDs on EULAR response.

Data were available from 11 studies comparing two or three interventions.

Figure 5 presents the network of evidence and Table 29 presents the frequency with which each pair of treatments was compared. No pair of treatments has been compared more than once. There are 12 treatment effects to estimate from 11 studies.

Figure 5: EULAR (Main Trials) – Network of evidence

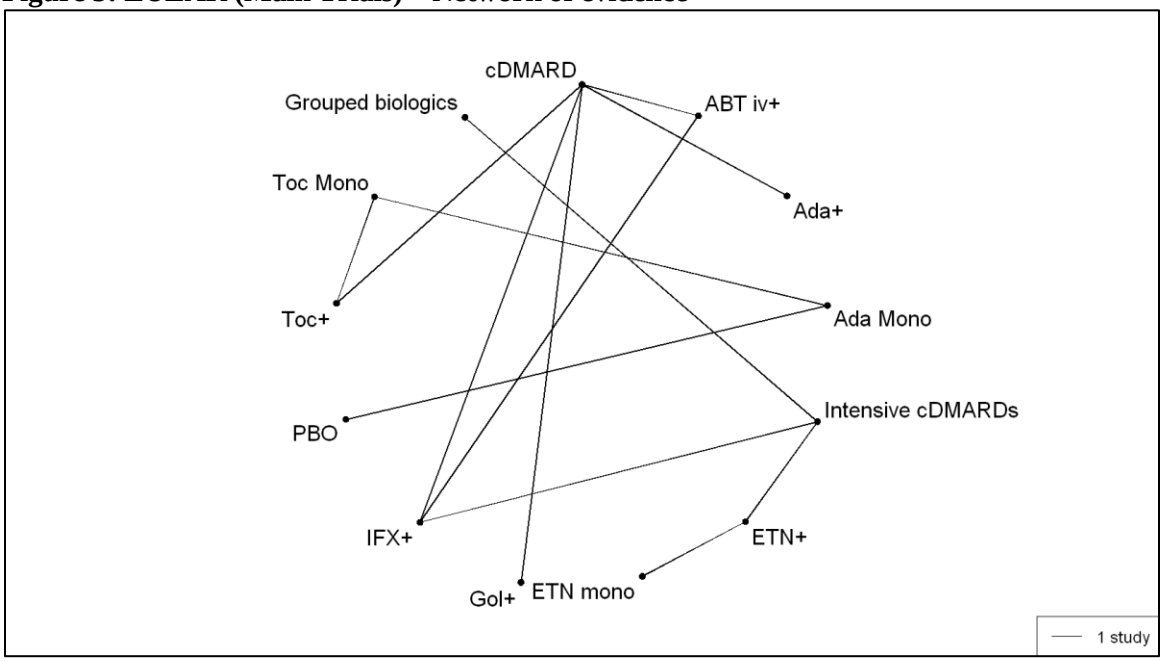


Table 29: EULAR (Main Trials) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ+	TCZ	Grouped Biologics
cDMARDs	-	1	1					1	1		1		
ABT iv+	-	-							1				
ADA+	-	-	-										
ADA	-	-	-	-						1		1	
Int cDMARDs	-	-	-	-	-	1			1				1
ETN+	-	-	-	-	-	-	1						
ETN	-	-	-	-	-	-	-						
Gol+	-	-	-	-	-	-	-	-					
IFX+	-	-	-	-	-	-	-	-	-				
PBO	-	-	-	-	-	-	-	-	-	-			
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1	
TCZ	-	-	-	-	-	-	-	-	-	-	-	-	
Grouped Biologics	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 30 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 31 presents the probabilities of treatment rankings.

The model fitted the data reasonably well, with the total residual deviance, 44.15, close to the total number of data points, 36, included in the analysis. The largest residual deviances were 9.4 (compared with 6 data points) for the ATTEST study and 8.2 (compared with 4 data points) for the JESMR study.

The between-study standard deviation was estimated to be 0.21 (95% CrI: 0.01, 0.71), which implies mild to moderate heterogeneity between studies in intervention effects.

All interventions except for PBO were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with TCZ+ and ETN+. However, the treatment effects were only statistically significant for Gol+ and TCZ+ at a conventional 5% level. ETN+ (Probability of being the best 0.381) and TCZ+ (Probability of being the best 0.372) were the treatments that were most likely to be the most effective interventions.

Table 30: EULAR (Main Trials) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.4974	0.3464	-0.4949	-1.2290, 0.2211
ADA+	-0.6454	0.3851	-0.6468	-1.4440, 0.1382
ADA	-0.1440	0.5749	-0.1385	-1.3730, 1.0640
Int cDMARDs	-0.0880	0.4959	-0.0890	-1.1210, 0.9493
ETN+	-1.1040	0.6090	-1.1030	-2.3510, 0.1858
ETN	-0.4137	0.7114	-0.4184	-1.8960, 1.0950
Gol+	-0.7803	0.3608	-0.7805	-1.5300, -0.0364
IFX+	-0.3777	0.3468	-0.3753	-1.0900, 0.3527
PBO	0.5659	0.6732	0.5671	-0.8365, 1.9940
TCZ+	-1.1490	0.3259	-1.1500	-1.8450, -0.4469
TCZ	-0.9177	0.4619	-0.9142	-1.9100, 0.0494
Grouped Biologics	-0.5415	0.6130	-0.5467	-1.8030, 0.7103
Between study SD	0.2499	0.1909	0.2105	0.0083, 0.7059

Table 31: EULAR (Main Trials) – Probability of treatment rankings

	Rank												
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13
cDMARDs	0.000	0.000	0.000	0.001	0.006	0.012	0.027	0.049	0.086	0.161	0.293	0.310	0.056
ABT iv+	0.009	0.018	0.033	0.067	0.122	0.188	0.194	0.154	0.101	0.063	0.030	0.014	0.007
ADA+	0.039	0.060	0.096	0.138	0.169	0.139	0.101	0.081	0.067	0.057	0.031	0.016	0.008
ADA	0.004	0.011	0.025	0.034	0.043	0.054	0.066	0.080	0.107	0.138	0.179	0.249	0.008
Int cDMARDs	0.000	0.001	0.006	0.013	0.018	0.029	0.042	0.064	0.111	0.226	0.213	0.205	0.071
ETN+	0.381	0.181	0.149	0.103	0.070	0.043	0.025	0.017	0.013	0.011	0.006	0.003	0.000
ETN	0.014	0.062	0.059	0.068	0.086	0.098	0.105	0.095	0.112	0.092	0.081	0.072	0.056
Gol+	0.066	0.092	0.158	0.194	0.156	0.111	0.074	0.054	0.039	0.029	0.016	0.008	0.003
IFX+	0.001	0.005	0.014	0.026	0.054	0.099	0.180	0.237	0.221	0.101	0.043	0.015	0.006
PBO	0.002	0.003	0.004	0.008	0.010	0.011	0.014	0.017	0.020	0.028	0.044	0.075	0.766
TCZ+	0.372	0.315	0.137	0.075	0.041	0.024	0.015	0.011	0.007	0.003	0.001	0.000	0.000
TCZ	0.083	0.191	0.241	0.174	0.108	0.065	0.039	0.033	0.026	0.023	0.015	0.001	0.000
Grouped Biologics	0.030	0.062	0.079	0.099	0.119	0.128	0.118	0.109	0.092	0.069	0.047	0.032	0.018

Table 32 and 33 present the probabilities of achieving at least a moderate response and at least a good response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 32: EULAR (Main Trials) – Probability of achieving at least moderate response

Intervention	Mean	SD	Median	95% CrI
cDMARDs	0.4765	0.0645	0.4768	0.3508, 0.6031
ABT iv+	0.6592	0.1277	0.6680	0.3655 ,0.8882
ADA+	0.7063	0.1315	0.7216	0.4027, 0.9239
ADA	0.5288	0.1876	0.5310	0.1252 ,0.9100
Int cDMARDs	0.5101	0.1741	0.5111	0.1470 ,0.8671
ETN+	0.8158	0.1495	0.8524	0.3939 ,0.9902
ETN	0.6164	0.2135	0.6395	0.1169 ,0.9677
Gol+	0.7491	0.1171	0.7641	0.4695 ,0.9373
IFX+	0.6171	0.1321	0.6242	0.3231 ,0.8644
PBO	0.2972	0.1893	0.2665	0.0199 ,0.7919
TCZ+	0.8478	0.0850	0.8617	0.6249 ,0.9674
TCZ	0.7821	0.1302	0.8040	0.4378 ,0.9703
Grouped Biologics	0.6614	0.1885	0.6862	0.2079 ,0.9618

Table 33: EULAR (Main Trials) – Probability of achieving at least good response

Intervention	Mean	SD	Median	
cDMARDs	0.1145	0.0399	0.1099	0.0511, 0.2064
ABT iv+	0.2479	0.1191	0.2325	0.0611 ,0.5396
ADA+	0.2957	0.1371	0.2804	0.0728 ,0.6175
ADA	0.1726	0.1425	0.1380	0.0094, 0.5748
Int cDMARDs	0.1552	0.1209	0.1263	0.0124, 0.4849
ETN+	0.4572	0.2015	0.4513	0.0733, 0.8820
ETN	0.2508	0.1900	0.2078	0.0092, 0.7569
Gol+	0.3386	0.1385	0.3262	0.1009, 0.6514
IFX+	0.2141	0.1112	0.1967	0.0482, 0.4851
PBO	0.0685	0.1050	0.0366	0.0006, 0.3668
TCZ+	0.4703	0.1379	0.4695	0.1892, 0.7627
TCZ	0.3891	0.1642	0.3777	0.0897, 0.7717
Grouped Biologics	0.2782	0.1791	0.2478	0.0229, 0.7320

5.3.2.2 EULAR – Main Trials plus Prior Biologics with AMBITION

A network meta-analysis was used to compare the effects of abatacept iv + MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo, tocilizumab (with and without MTX) and the grouped biologics from TACIT RCT and certolizumab pegol + MTX relative to cDMARDs on EULAR response.

Data were available from 15 studies comparing two or three interventions.

Figure 6 presents the network of evidence and Table 34 presents the frequency with which each pair of treatments was compared. Only tocilizumab + MTX and certolizumab + MTX have been compared more than once and these were both against cDMARDs. There are 13 treatment effects to estimate from 15 studies.

Figure 6: EULAR (Main Trials plus Prior Biologics with AMBITION) – Network of evidence

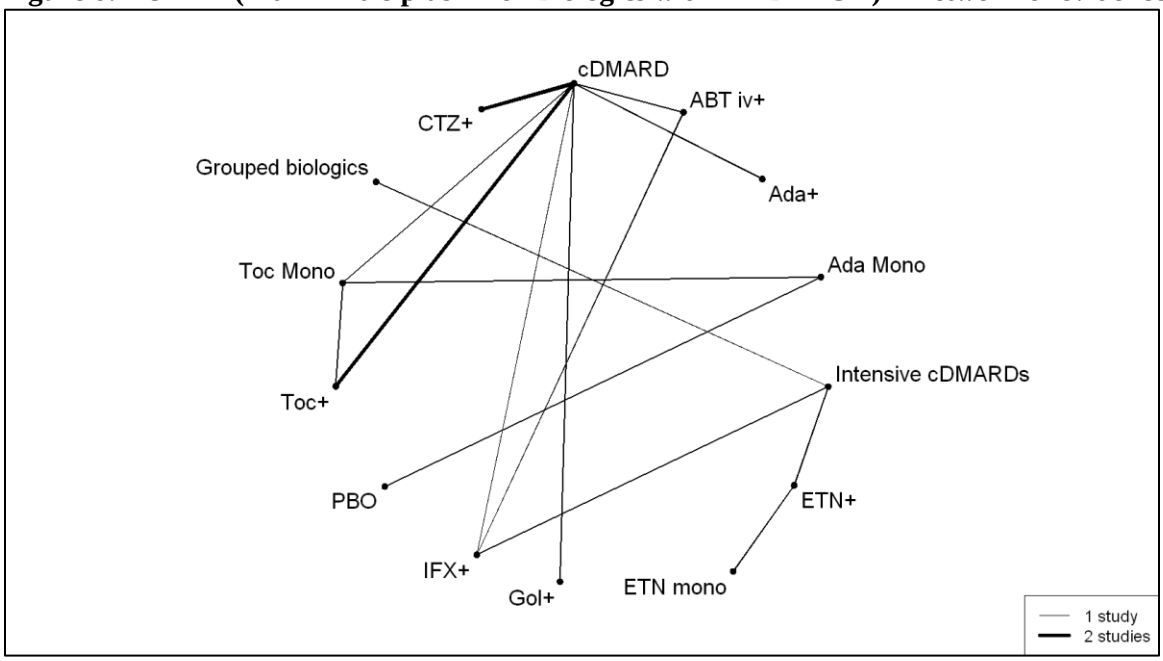


Table 35 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 36 presents the probabilities of treatment rankings.

Table 34: EULAR (Main Trials plus Prior Biologics with AMBITION) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ+	TCZ	Grouped Bios	CTZ+
cDMARDs	-	1	1					1	1		2	1		2
ABT iv+	-	-							1					
ADA+	-	-	-											
ADA	-	-	-	-						1		1		
Int cDMARDs	-	-	-	-	-	1			1				1	
ETN+	-	-	-	-	-	-	1							
ETN	-	-	-	-	-	-	-							
Gol+	-	-	-	-	-	-	-	-						
IFX+	-	-	-	-	-	-	-	-	-					
PBO	-	-	-	-	-	-	-	-	-	-				
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1		
TCZ	-	-	-	-	-	-	-	-	-	-	-	-		
Grouped Bios	-	-	-	-	-	-	-	-	-	-	-	-	-	
CTZ+	-	-	-	-	-	-	-	-	-	-	-	-	-	-

The model fitted the data moderately well, with the total residual deviance, 59.95, close to the total number of data points, 48, included in the analysis. The largest residual deviances were 9.4 (compared with 6 data points) for the ATTEST study, 8.1 (compared with 4 data points) for the JESMR study and 7.2 (compared with 4 data points) for the OPTION study.

The between-study standard deviation was estimated to be 0.14 (95% CrI: 0.01, 0.46), which implies mild heterogeneity between studies in intervention effects. The inclusion of the additional studies has reduced the uncertainty in the between study standard deviation.

All interventions except for adalimumab and placebo were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with certolizumab + MTX, tocilizumab + MTX and etanercept + MTX. The treatment effects were statistically significant for seven of the 13 interventions at a conventional 5% level, namely abatacept iv + MTX, adalimumab + MTX, etanercept + MTX, golimumab + MTX, tocilizumab + MTX, tocilizumab and certolizumab + MTX. Certolizumab + MTX (probability of being the best 0.793) and etanercept + MTX (probability of being the best 0.153) were the treatments that were most likely to be the most effective interventions. The inclusion of the additional studies has reduced the uncertainty associated with each treatment effect, and has shrunk the adalimumab effect towards the cDMARD response, worsened the effect of placebo and reduced the effect of tocilizumab. The additional studies also included certolizumab + MTX, which is likely to be the most effective treatment of these interventions in this population.

Table 35: EULAR (Main Trials plus Prior Biologics with AMBITION) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.5036	0.2505	-0.5039	-1.0160, -0.0055
ADA+	-0.6521	0.2983	-0.6496	-1.2480, -0.0682
ADA	0.0109	0.3009	0.0125	-0.6029, 0.6174
Int cDMARDs	-0.0928	0.3655	-0.0921	-0.8132, 0.6252
ETN+	-1.1080	0.4456	-1.1080	-1.9830, -0.2280
ETN	-0.4143	0.5280	-0.4147	-1.4550, 0.6330
Gol+	-0.7805	0.2711	-0.7817	-1.3220, -0.2470
IFX+	-0.3827	0.2500	-0.3809	-0.8936, 0.1102
PBO	0.7218	0.4011	0.7290	-0.0845, 1.5190
TCZ+	-1.1480	0.1439	-1.1470	-1.4480, -0.8545
TCZ	-0.7733	0.1747	-0.7720	-1.1390, -0.4287
Grouped biologics	-0.5475	0.4554	-0.5499	-1.4480, 0.3466
CTZ+	-1.5210	0.1837	-1.5190	-1.8980, -1.1590
Between study SD	0.1669	0.1178	0.1442	0.0102, 0.4596

Table 36: EULAR (Main Trials plus Prior Biologics with AMBITION) – Probability of treatment rankings

	Rank													
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14
cDMARDs	0.000	0.000	0.000	0.000	0.000	0.001	0.004	0.013	0.034	0.092	0.181	0.402	0.256	0.016
ABT iv+	0.001	0.004	0.011	0.030	0.070	0.132	0.219	0.215	0.163	0.089	0.047	0.013	0.005	0.002
ADA+	0.005	0.025	0.068	0.129	0.145	0.164	0.136	0.104	0.085	0.067	0.051	0.014	0.006	0.001
ADA	0.000	0.001	0.001	0.004	0.006	0.014	0.023	0.033	0.054	0.095	0.148	0.225	0.393	0.003
Int cDMARDs	0.000	0.000	0.001	0.002	0.006	0.009	0.016	0.030	0.055	0.136	0.311	0.193	0.208	0.032
ETN+	0.153	0.284	0.234	0.125	0.081	0.062	0.029	0.014	0.007	0.005	0.003	0.001	0.000	0.000
ETN	0.004	0.017	0.038	0.064	0.069	0.085	0.104	0.108	0.116	0.140	0.092	0.072	0.066	0.026
Gol+	0.008	0.046	0.127	0.194	0.192	0.159	0.103	0.066	0.044	0.032	0.022	0.005	0.002	0.000
IFX+	0.000	0.001	0.002	0.008	0.018	0.040	0.103	0.218	0.287	0.223	0.075	0.019	0.007	0.001
PBO	0.000	0.000	0.000	0.000	0.001	0.001	0.002	0.003	0.004	0.006	0.009	0.019	0.040	0.913
TCZ+	0.027	0.445	0.349	0.111	0.040	0.016	0.007	0.003	0.001	0.001	0.000	0.000	0.000	0.000
TCZ	0.001	0.008	0.086	0.220	0.263	0.200	0.110	0.056	0.028	0.017	0.010	0.001	0.000	0.000
Grouped Bios	0.007	0.019	0.049	0.100	0.105	0.114	0.144	0.135	0.121	0.098	0.051	0.035	0.016	0.006
CTZ+	0.793	0.149	0.035	0.013	0.004	0.002	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000

Table 37 and 38 present the probabilities of achieving at least a moderate response and at least a good response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 37: EULAR (Main Trials plus Prior Biologics with AMBITION) – Probability of achieving at least moderate response

	Mean	SD	Median	95% CrI
cDMARDs	0.4360	0.0548	0.4346	0.3306, 0.5453
ABT iv+	0.6285	0.1034	0.6334	0.4065, 0.8186
ADA+	0.6790	0.1118	0.6873	0.4388, 0.8723
ADA	0.4343	0.1210	0.4308	0.2026, 0.6860
Int cDMARDs	0.4739	0.1409	0.4729	0.2039, 0.7569
ETN+	0.8055	0.1197	0.8282	0.5102, 0.9682
ETN	0.5881	0.1803	0.6004	0.2008, 0.9089
Gol+	0.7228	0.0980	0.7321	0.5034, 0.8895
IFX+	0.5837	0.1063	0.5863	0.3659, 0.7861
PBO	0.2069	0.1152	0.1868	0.0419, 0.4883
TCZ+	0.8331	0.0496	0.8372	0.7239, 0.9176
TCZ	0.7243	0.0726	0.7284	0.5698, 0.8559
Grouped Bios	0.6367	0.1578	0.6505	0.2888, 0.9058
CTZ+	0.9071	0.0387	0.9125	0.8164, 0.9655

Table 38: EULAR (Main Trials plus Prior Biologics with AMBITION) – Probability of achieving at least good response

	Mean	SD	Median	95% CrI
cDMARDs	0.0900	0.0268	0.0869	0.0462, 0.1511
ABT iv+	0.2061	0.0829	0.1964	0.0731, 0.3983
ADA+	0.2516	0.1041	0.2393	0.0839, 0.4856
ADA	0.0973	0.0615	0.0852	0.0198, 0.2469
Int cDMARDs	0.1193	0.0790	0.1034	0.0205, 0.3129
ETN+	0.4098	0.1616	0.4027	0.1172, 0.7507
ETN	0.2022	0.1404	0.1734	0.0199, 0.5567
Gol+	0.2905	0.1041	0.2816	0.1136, 0.5182
IFX+	0.1747	0.0756	0.1645	0.0580, 0.3515
PBO	0.0284	0.0359	0.0185	0.0016, 0.1122
TCZ+	0.4184	0.0829	0.4163	0.2645, 0.5867
TCZ	0.2844	0.0795	0.2786	0.1453, 0.4576
Grouped Bios	0.2313	0.1340	0.2091	0.0382, 0.5509
CTZ+	0.5624	0.0943	0.5625	0.3716, 0.7441

5.3.2.3 EULAR – Main Trials plus Prior Biologics without AMBITION

A network meta-analysis was used to compare the effects of abatacept iv + MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo, tocilizumab (with and without MTX) and the grouped biologics from TACIT RCT and certolizumab pegol + MTX relative to cDMARDs on EULAR response

Data were available from 14 studies comparing two or three interventions.

Figure 7 presents the network of evidence and Table 39 presents the frequency with which each pair of treatments was compared. Only tocilizumab + MTX and certolizumab + MTX have been compared more than once and these were both against cDMARDs. There are 13 treatment effects to estimate from 14 studies.

Figure 7: EULAR (Main Trials plus Prior Biologics without AMBITION) – Network of evidence

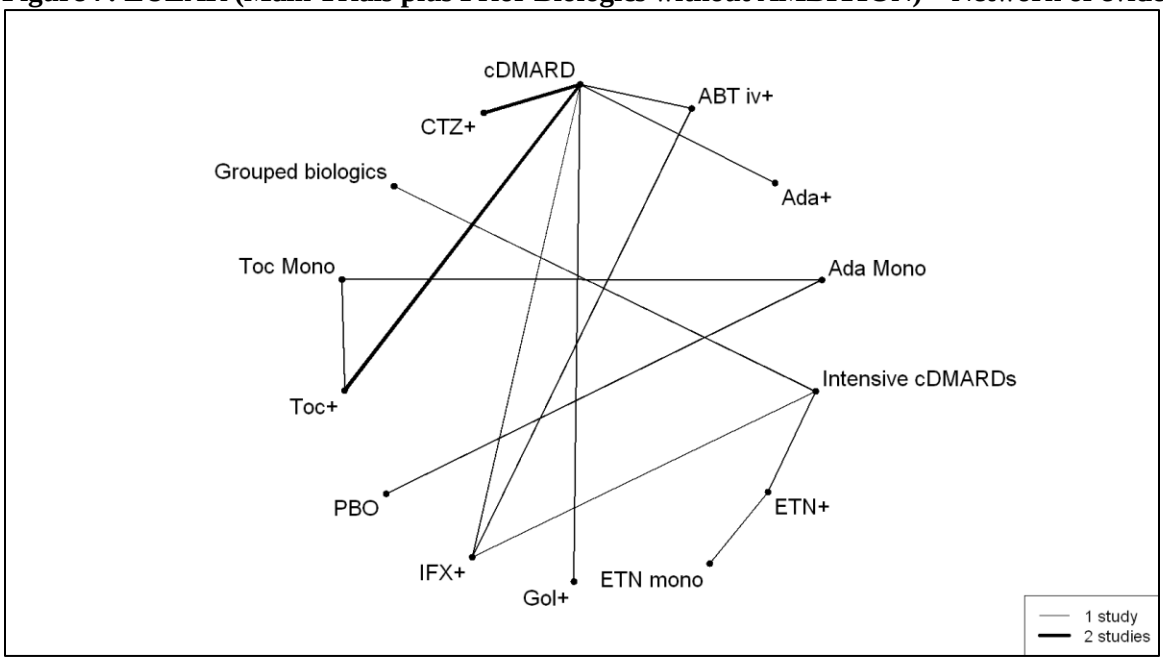


Table 39: EULAR (Main Trials plus Prior Biologics without AMBITION) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ +	TCZ	Grouped Bios	CTZ +
cDMARDs	-	1	1					1	1		2			2
ABT iv+	-	-							1					
ADA+	-	-	-											
ADA	-	-	-	-						1		1		
Int cDMARDs	-	-	-	-	-	1			1				1	
ETN+	-	-	-	-	-	-	1							
ETN	-	-	-	-	-	-	-							
Gol+	-	-	-	-	-	-	-	-						
IFX+	-	-	-	-	-	-	-	-	-					
PBO	-	-	-	-	-	-	-	-	-	-				
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1		
TCZ	-	-	-	-	-	-	-	-	-	-	-	-		
Grouped biologics	-	-	-	-	-	-	-	-	-	-	-	-	-	
CTZ+	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 40 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 41 presents the probabilities of treatment rankings.

The model fitted the data moderately well, with the total residual deviance, 54.49, close to the total number of data points, 44, included in the analysis. The largest residual deviances were 9.4 (compared with 6 data points) for the ATTEST study and 8.1 (compared with 4 data points) for the JESMR study.

The between-study standard deviation was estimated to be 0.11 (95% CrI: 0.01, 0.48), which implies mild heterogeneity between studies in intervention effects. Excluding the AMBITION study had little impact on the estimate of the bewteen study standard deviation.

All interventions except for PBO were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with certolizumab pegol + MTX, tocilizumab + MTX and etanercept + MTX. The treatment effects were statistically significant for seven of the 13 interventions at a conventional 5% level, namely abatacept iv+ MTX, adalimumab + MTX, etanercept + MTX, golimumab + MTX, tocilizumab + MTX, tocilizumab and certolizumab pegol + MTX. Certolizumab pegol + MTX (probability of being the best 0.786) and etanercept + MTX (probability of being the best 0.133) were the treatments that were most likely to be the most effective interventions. The exclusion of the AMBITION study has resulted in a slight increase in the effects of adalimumab, placebo and tocilizumab relative to cDMARDs.

Table 40: EULAR (Main Trials plus Prior Biologics without AMBITION) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.4994	0.2439	-0.4982	-0.9877, -0.0177
ADA+	-0.6442	0.2948	-0.6415	-1.2300, -0.0670
ADA	-0.1971	0.3561	-0.1943	-0.9267, 0.5205
Int cDMARDs	-0.0850	0.3500	-0.0818	-0.7974, 0.5962
ETN+	-1.1020	0.4292	-1.1050	-1.9660, -0.2551
ETN	-0.4101	0.5098	-0.4123	-1.4290, 0.5926
Gol+	-0.7815	0.2619	-0.7782	-1.3030, -0.2639
IFX+	-0.3757	0.2395	-0.3734	-0.8724, 0.0974
PBO	0.5088	0.4341	0.5122	-0.3724, 1.3810
TCZ+	-1.2150	0.1551	-1.2100	-1.5440, -0.9106
TCZ	-0.9788	0.2712	-0.9782	-1.5480, -0.4306
Grouped bios	-0.5396	0.4422	-0.5370	-1.4250, 0.3124
CTZ+	-1.5160	0.1781	-1.5120	-1.8840, -1.1670
Between study SD	0.1463	0.1266	0.1124	0.0054, 0.4815

Table 41: EULAR (Main Trials plus Prior Biologics without AMBITION) – Probability of treatment rankings

	Rank													
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14
cDMARDs	0.000	0.000	0.000	0.000	0.000	0.001	0.004	0.008	0.022	0.063	0.147	0.306	0.406	0.043
ABT iv+	0.001	0.002	0.006	0.020	0.053	0.128	0.220	0.223	0.173	0.096	0.050	0.020	0.006	0.002
ADA+	0.004	0.015	0.040	0.094	0.156	0.196	0.150	0.108	0.086	0.068	0.052	0.022	0.008	0.002
ADA	0.001	0.002	0.003	0.010	0.021	0.037	0.060	0.083	0.096	0.132	0.180	0.201	0.172	0.002
Int cDMARDs	0.000	0.000	0.001	0.002	0.004	0.007	0.014	0.024	0.046	0.099	0.240	0.251	0.247	0.065
ETN+	0.133	0.232	0.204	0.181	0.118	0.067	0.032	0.014	0.008	0.006	0.003	0.002	0.001	0.000
ETN	0.003	0.015	0.024	0.040	0.073	0.100	0.108	0.110	0.107	0.130	0.110	0.082	0.065	0.035
Gol+	0.006	0.030	0.076	0.165	0.241	0.193	0.120	0.071	0.041	0.029	0.019	0.007	0.003	0.001
IFX+	0.000	0.000	0.001	0.004	0.011	0.031	0.085	0.187	0.278	0.252	0.109	0.030	0.008	0.002
PBO	0.000	0.000	0.001	0.001	0.002	0.003	0.005	0.006	0.008	0.012	0.019	0.035	0.066	0.840
TCZ+	0.039	0.500	0.321	0.086	0.030	0.012	0.006	0.003	0.001	0.001	0.000	0.000	0.000	0.000
TCZ	0.020	0.052	0.249	0.320	0.179	0.088	0.040	0.022	0.013	0.009	0.006	0.002	0.000	0.000
Grouped Bios	0.007	0.014	0.032	0.058	0.104	0.137	0.156	0.139	0.119	0.104	0.064	0.041	0.017	0.006
CTZ+	0.786	0.138	0.043	0.018	0.008	0.003	0.002	0.001	0.000	0.000	0.000	0.000	0.000	0.000

Table 42 and 43 present the probabilities of achieving at least a moderate response and at least a good response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 42: EULAR (Main Trials plus Prior Biologics without AMBITION) – Probability of achieving at least moderate response

	Mean	SD	Median	95% CrI
cDMARDs	0.4023	0.0496	0.4013	0.3076, 0.5011
ABT iv+	0.5952	0.1014	0.5983	0.3850, 0.7881
ADA+	0.6465	0.1126	0.6526	0.4052, 0.8481
ADA	0.4799	0.1337	0.4774	0.2107, 0.7609
Int cDMARDs	0.4382	0.1339	0.4332	0.1869, 0.7199
ETN+	0.7828	0.1216	0.8032	0.4832, 0.9605
ETN	0.5570	0.1767	0.5632	0.1919, 0.8876
Gol+	0.6954	0.0975	0.7015	0.4821, 0.8668
IFX+	0.5484	0.1023	0.5501	0.3436, 0.7507
PBO	0.2429	0.1296	0.2233	0.0505, 0.5651
TCZ+	0.8282	0.0510	0.8328	0.7159, 0.9145
TCZ	0.7581	0.0891	0.7663	0.5561, 0.9100
Grouped Bios	0.6042	0.1551	0.6117	0.2760, 0.8888
CTZ+	0.8919	0.0411	0.8968	0.7986, 0.9557

Table 43: EULAR (Main Trials plus Prior Biologics without AMBITION) – Probability of achieving at least good response

	Mean	SD	Median	95% CrI
cDMARDs	0.0796	0.0242	0.0770	0.0396, 0.1339
ABT iv+	0.1866	0.0773	0.1772	0.0652, 0.3660
ADA+	0.2289	0.0985	0.2168	0.0724, 0.4545
ADA	0.1250	0.0824	0.1088	0.0228, 0.3277
Int cDMARDs	0.1049	0.0732	0.0895	0.0180, 0.2872
ETN+	0.3829	0.1549	0.3729	0.1096, 0.7252
ETN	0.1833	0.1312	0.1545	0.0184, 0.5243
Gol+	0.2685	0.0975	0.2589	0.1051, 0.4872
IFX+	0.1562	0.0692	0.1467	0.0521, 0.3205
PBO	0.0396	0.0512	0.0262	0.0023, 0.1629
TCZ+	0.4182	0.0849	0.4166	0.2571, 0.5934
TCZ	0.3342	0.1075	0.3268	0.1409, 0.5765
Grouped Bios	0.2094	0.1263	0.1866	0.0365, 0.5234
CTZ+	0.5343	0.0927	0.5352	0.3481, 0.7151

5.3.2.4 ACR – Main Trials

A network meta-analysis was used to compare the effects of abatacept iv +, MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo, tocilizumab (with and without MTX), certolizumab pegol + MTX, and abatacept sc + MTX relative to cDMARDs on ACR response.

Data were available from 28 studies comparing two or three interventions.

Figure 8 presents the network of evidence and Table 44 presents the frequency with which each pair of treatments was compared. There were 13 treatment effects to estimate from 28 studies.

Figure 8: ACR (Main Trials) – Network of evidence

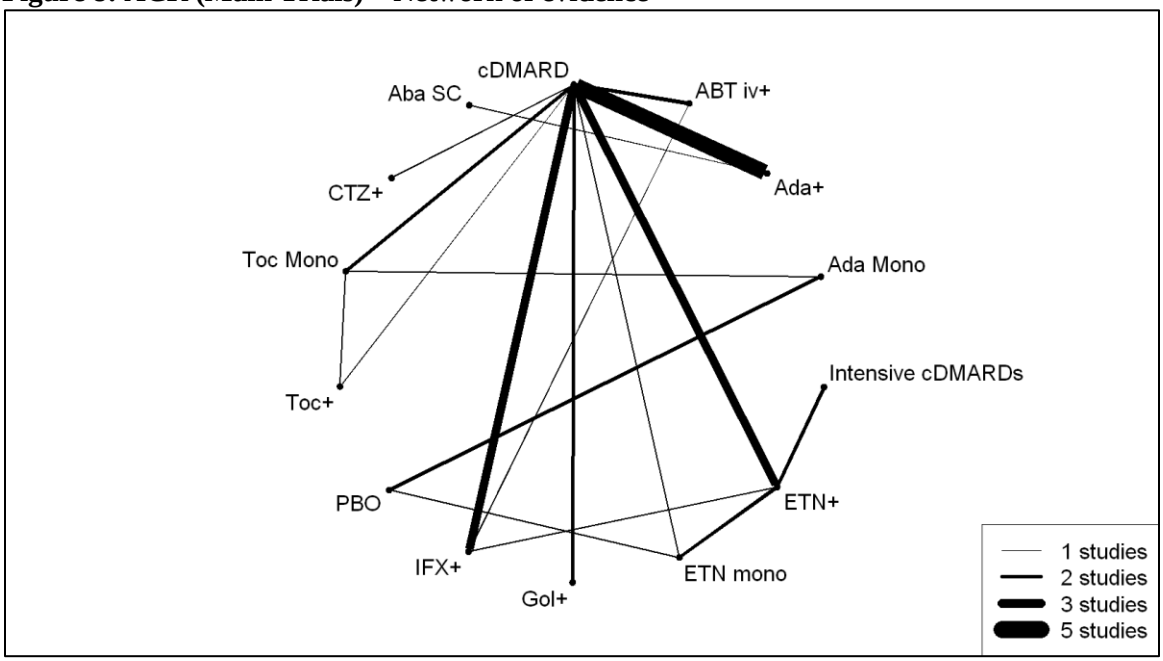


Table 44: ACR (Main Trials) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ+	TCZ	CTZ+	ABA sc+
cDMARDs	-	2	5			3	1	2	3		1	2	1	
ABT iv+	-	-							1					
ADA+	-	-	-											1
ADA	-	-	-	-						2		1		
Int cDMARDs	-	-	-	-	-	2								
ETN+	-	-	-	-	-	-	2		1					
ETN	-	-	-	-	-	-	-			1				
Gol+	-	-	-	-	-	-	-	-						
IFX+	-	-	-	-	-	-	-	-	-					
PBO	-	-	-	-	-	-	-	-	-	-				
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1		
TCZ	-	-	-	-	-	-	-	-	-	-	-	-		
CTZ+	-	-	-	-	-	-	-	-	-	-	-	-	-	
ABA sc+	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 45 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 46 presents the probabilities of treatment rankings.

The model fitted the data reasonably well, with the total residual deviance, 191.50, close to the total number of data points, 174, included in the analysis. The largest residual deviances were 16.9 (compared with 6 data points) for the O'Dell study, 11.9 (compared with 6 data points) for the ARMADA study, 11.7 (compared with 6 data points) for the SATORI study and 10.7 (compared with 6 data points) for the ADACTA study.

The between-study standard deviation was estimated to be 0.24 (95% CrI: 0.13, 0.40), which implies mild heterogeneity between studies in intervention effects.

All interventions except for PBO were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with etanercept + MTX, tocilizumab (with and without MTX). The treatment effects were statistically significant for all interventions except for adalimumab and placebo at a conventional 5% level. Etanercept + MTX (probability of being the best 0.273), TCZ (Probability of being the best 0.221) and tocilizumab + MTX (probability of being the best 0.206) were the treatments that were most likely to be the most effective interventions.

Table 45: ACR (Main Trials) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.7180	0.1873	-0.7183	-1.0910, -0.3467
ADA+	-0.8250	0.1347	-0.8223	-1.0970, -0.5636
ADA	-0.5149	0.2740	-0.5157	-1.0540, 0.0276
Int cDMARDs	-0.5364	0.2632	-0.5364	-1.0520, -0.0112
ETN+	-1.0940	0.1749	-1.0950	-1.4360, -0.7532
ETN	-0.9038	0.2198	-0.9053	-1.3350, -0.4648
Gol+	-0.8916	0.2141	-0.8920	-1.3130, -0.4705
IFX+	-0.7732	0.1552	-0.7707	-1.0870, -0.4735
PBO	0.4143	0.2892	0.4125	-0.1523, 0.9914
TCZ+	-1.0620	0.2086	-1.0610	-1.4800, -0.6435
TCZ	-1.0870	0.1774	-1.0860	-1.4400, -0.7382
CTZ+	-0.6435	0.3182	-0.6449	-1.2840, -0.0102
ABA sc+	-0.8851	0.2985	-0.8802	-1.4900, -0.2989
Between study SD	0.2449	0.0689	0.2360	0.1334, 0.4008

Table 46: ACR (Main Trials) – Probability of treatment rankings

	Rank													
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14
cDMARDs	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.069	0.858	0.069
ABT iv+	0.007	0.013	0.027	0.041	0.062	0.090	0.110	0.138	0.166	0.162	0.126	0.057	0.001	0.000
ADA+	0.005	0.022	0.042	0.079	0.128	0.169	0.178	0.161	0.116	0.069	0.027	0.005	0.000	0.000
ADA	0.002	0.005	0.010	0.014	0.027	0.036	0.045	0.060	0.086	0.140	0.233	0.312	0.030	0.000
Int cDMARDs	0.001	0.006	0.011	0.017	0.027	0.036	0.049	0.065	0.094	0.154	0.244	0.272	0.021	0.003
ETN+	0.273	0.213	0.191	0.135	0.083	0.050	0.029	0.015	0.007	0.003	0.000	0.000	0.000	0.000
ETN	0.046	0.088	0.109	0.137	0.136	0.114	0.104	0.095	0.081	0.062	0.024	0.005	0.000	0.000
Gol+	0.072	0.082	0.097	0.117	0.121	0.114	0.105	0.091	0.080	0.064	0.040	0.017	0.000	0.000
IFX+	0.007	0.014	0.030	0.052	0.090	0.126	0.148	0.170	0.163	0.121	0.061	0.018	0.000	0.000
PBO	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.009	0.066	0.923
TCZ+	0.206	0.203	0.169	0.137	0.097	0.065	0.047	0.032	0.023	0.012	0.007	0.002	0.000	0.000
TCZ	0.221	0.243	0.191	0.139	0.087	0.051	0.032	0.020	0.010	0.004	0.001	0.000	0.000	0.000
CTZ+	0.035	0.030	0.038	0.041	0.051	0.059	0.066	0.074	0.094	0.133	0.164	0.190	0.021	0.004
ABA sc+	0.125	0.081	0.086	0.091	0.092	0.094	0.086	0.078	0.080	0.076	0.064	0.044	0.003	0.001

Table 47, 48 and 49 present the probabilities of achieving at least an ACR20 response, at least an ACR50 response and at least an ACR70 response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 47: ACR (Main Trials) – Probability of achieving at least ACR20

	Mean	SD	Median	95% CrI
cDMARDs	0.3008	0.0224	0.3004	0.2577, 0.3457
ABT iv+	0.5757	0.0761	0.5779	0.4220, 0.7216
ADA+	0.6173	0.0563	0.6181	0.5042, 0.7266
ADA	0.4968	0.1075	0.4979	0.2860, 0.7099
Int cDMARDs	0.5051	0.1038	0.5056	0.2989, 0.7074
ETN+	0.7127	0.0625	0.7160	0.5818, 0.8250
ETN	0.6447	0.0832	0.6488	0.4716, 0.7967
Gol+	0.6404	0.0816	0.6440	0.4695, 0.7909
IFX+	0.5973	0.0638	0.5979	0.4702, 0.7224
PBO	0.1843	0.0767	0.1750	0.0631, 0.3624
TCZ+	0.7006	0.0743	0.7051	0.5405, 0.8353
TCZ	0.7103	0.0633	0.7135	0.5773, 0.8267
CTZ+	0.5455	0.1221	0.5480	0.3013, 0.7797
ABA sc+	0.6353	0.1090	0.6393	0.4069, 0.8375

Table 48: ACR (Main Trials) – Probability of achieving at least ACR50

	Mean	SD	Median	95% CrI
cDMARDs	0.1254	0.0139	0.1249	0.0996, 0.1543
ABT iv+	0.3355	0.0712	0.3336	0.2052, 0.4841
ADA+	0.3735	0.0564	0.3717	0.2682, 0.4918
ADA	0.2701	0.0901	0.2634	0.1155, 0.4700
Int cDMARDs	0.2765	0.0879	0.2698	0.1243, 0.4672
ETN+	0.4777	0.0730	0.4775	0.3367, 0.6210
ETN	0.4048	0.0864	0.4029	0.2416, 0.5794
Gol+	0.4001	0.0844	0.3982	0.2403, 0.5738
IFX+	0.3547	0.0621	0.3516	0.2397, 0.4840
PBO	0.0667	0.0387	0.0591	0.0155, 0.1633
TCZ+	0.4653	0.0848	0.4648	0.2995, 0.6367
TCZ	0.4749	0.0738	0.4745	0.3307, 0.6222
CTZ+	0.3146	0.1103	0.3060	0.1242, 0.5574
ABA sc+	0.3995	0.1127	0.3929	0.1936, 0.6399

Table 49: ACR (Main Trials) – Probability of achieving at least ACR70

	Mean	SD	Median	95% CrI
cDMARDs	0.0432	0.0063	0.0428	0.0320, 0.0565
ABT iv+	0.1632	0.0487	0.1590	0.0817, 0.2724
ADA+	0.1884	0.0406	0.1853	0.1178, 0.2783
ADA	0.1233	0.0570	0.1148	0.0389, 0.2599
Int cDMARDs	0.1269	0.0559	0.1189	0.0424, 0.2586
ETN+	0.2696	0.0609	0.2661	0.1604, 0.3981
ETN	0.2135	0.0655	0.2081	0.1022, 0.3572
Gol+	0.2098	0.0635	0.2043	0.1014, 0.3515
IFX+	0.1756	0.0437	0.1716	0.1018, 0.2721
PBO	0.0204	0.0156	0.0166	0.0032, 0.0608
TCZ+	0.2606	0.0698	0.2557	0.1369, 0.4128
TCZ	0.2674	0.0615	0.2636	0.1580, 0.4001
CTZ+	0.1533	0.0755	0.1414	0.0427, 0.3359
ABA sc+	0.2125	0.0868	0.2008	0.0759, 0.4177

5.3.2.5 ACR – Main Trials plus Prior Biologics with AMBITION

A network meta-analysis was used to compare the effects of abatacept iv +, MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo, tocilizumab (with and without MTX), certolizumab pegol + MTX, abatacept sc +, tofacitinib (5mg and 10mg doses) and MTX relative to cDMARDs on ACR response.

Data were available from 40 studies comparing two, three or four interventions.

Figure 9 presents the network of evidence and Table 50 presents the frequency with which each pair of treatments was compared. There were 15 treatment effects to estimate from 40 studies.

Figure 9: ACR (Main Trials plus Prior Biologics with AMBITION) – Network of evidence

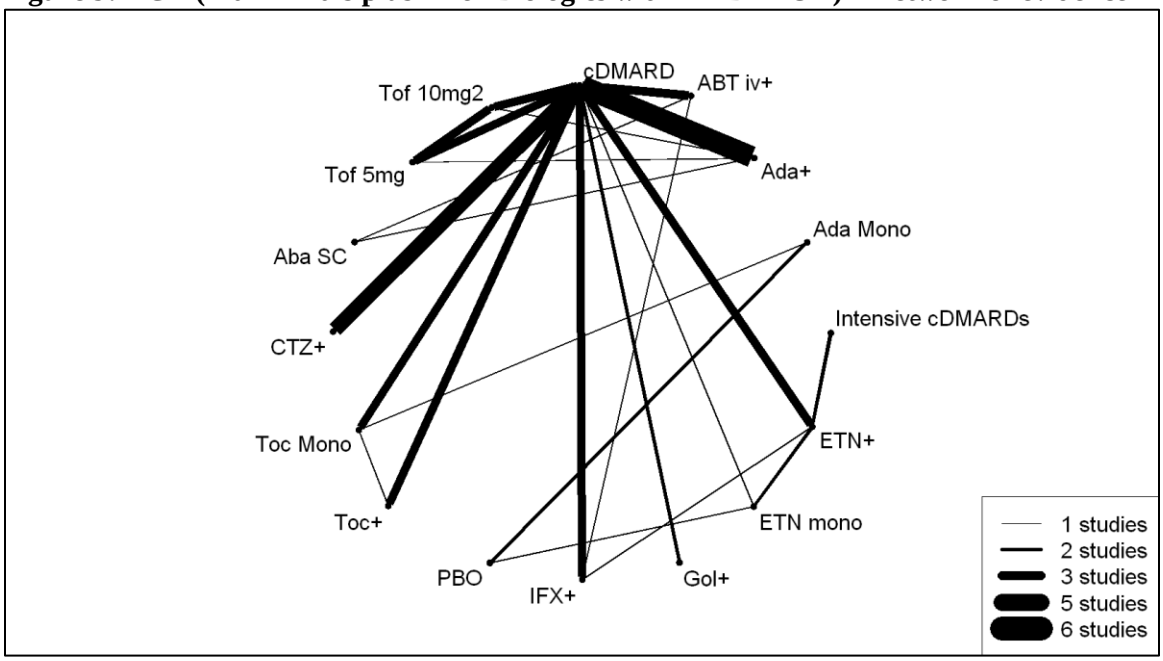


Table 50: ACR (Main Trials plus Prior Biologics with AMBITION) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ+	TCZ	CTZ+	ABA sc+	TOF 5mg	TOF 10mg
cDMARDs	-	3	6			3	1	2	3		3	3	5		3	3
ABT iv+	-	-							1					1		
ADA+	-	-	-											1	1	1
ADA	-	-	-	-						2		1				
Int cDMARDs	-	-	-	-	-	2										
ETN+	-	-	-	-	-	-	2		1							
ETN	-	-	-	-	-	-	-			1						
Gol+	-	-	-	-	-	-	-	-								
IFX+	-	-	-	-	-	-	-	-	-							
PBO	-	-	-	-	-	-	-	-	-	-						
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1				
TCZ	-	-	-	-	-	-	-	-	-	-	-	-				
CTZ+	-	-	-	-	-	-	-	-	-	-	-	-	-			
ABA sc+	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
TOF 5mg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
TOF 10mg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 51 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 52 presents the probabilities of treatment rankings.

There was some suggestion that model was not a good fit to all of the data, with the total residual deviance, 297.80, being larger than the total number of data points, 250, included in the analysis. However, the largest residual deviance, 34.8 (compared with 9 data points) was from the Kramer study and the deviance is likely to be a consequence of there being only one patient who had an ACR20 response and two patients who had an ACR50 response when treated with cDMARDS rather than a genuine lack of fit. The next largest residual deviances were 16.2 (compared with 6 data points) for the O'Dell study, 11.9 (compared with 6 data points) for the SATORI study, 10.7 (compared with 6 data points) for the ARMADA study, 10.1 (compared with 6 data points) for the JESMR study and 10.1 (compared with 6 data points) for the AMBITION study.

The between-study standard deviation was estimated to be 0.21 (95% CrI: 0.14, 0.32), which implies mild heterogeneity between studies in intervention effects. The inclusion of the additional studies has slightly reduced the uncertainty in the between study standard deviation.

All interventions except for placebo were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with certolizumab + MTX and etanercept + MTX. The treatment effects were statistically significant for all interventions except for adalimumab and placebo at a conventional 5% level. Certolizumab + MTX (probability of being the best 0.517) and etanercept + MTX (probability of being the best 0.273) were the treatments that were most likely to be the most effective interventions. The inclusion of the additional studies has had a small impact on six of the treatment effects. However, the effects of adalimumab (with and without MTX) tocilizumab (with and without MTX), ABA sc + MTX and placebo were smaller, and the effect of certolizumab + MTX were larger relative to cDMARDs.

Table 51: ACR (Main Trials plus Prior Biologics with AMBITION) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.7290	0.1325	-0.7280	-0.9932, -0.4705
ADA+	-0.7569	0.1043	-0.7558	-0.9665, -0.5565
ADA	-0.4035	0.2417	-0.4026	-0.8806, 0.0714
Int cDMARDs	-0.5175	0.2413	-0.5188	-0.9937, -0.0450
ETN+	-1.0800	0.1635	-1.0810	-1.4020, -0.7541
ETN	-0.8745	0.2049	-0.8754	-1.2750, -0.4699
Gol+	-0.8881	0.1986	-0.8881	-1.2770, -0.4984
IFX+	-0.7726	0.1387	-0.7712	-1.0510, -0.5029
PBO	0.4928	0.2624	0.4926	-0.0212, 1.0090
TCZ+	-0.9310	0.1250	-0.9305	-1.1810, -0.6876
TCZ	-0.9195	0.1350	-0.9185	-1.1880, -0.6518
CTZ+	-1.1570	0.1279	-1.1580	-1.4120, -0.9058
ABA sc+	-0.7910	0.1877	-0.7891	-1.1600, -0.4193
TOF 5mg	-0.6886	0.1483	-0.6894	-0.9796, -0.3949
TOF 10mg	-0.8208	0.1492	-0.8207	-1.1140, -0.5243
Between study SD	0.2173	0.0472	0.2137	0.1354, 0.3197

Table 53, 54 and 55 present the probabilities of achieving at least an ACR20 response, at least an ACR50 response and at least an ACR70 response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs “No response” rate.

Table 52: ACR (Main Trials plus Prior Biologics with AMBITION) – Probability of treatment rankings

	Rank															
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
cDMARDs	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.060	0.909	0.029
ABT iv+	0.001	0.006	0.014	0.024	0.043	0.061	0.084	0.108	0.126	0.144	0.152	0.142	0.075	0.019	0.000	0.000
ADA+	0.001	0.003	0.010	0.024	0.046	0.075	0.112	0.142	0.161	0.159	0.135	0.091	0.035	0.006	0.000	0.000
ADA	0.001	0.001	0.003	0.004	0.005	0.009	0.014	0.017	0.021	0.027	0.039	0.073	0.222	0.518	0.046	0.000
Int cDMARDs	0.001	0.004	0.009	0.013	0.019	0.022	0.029	0.032	0.039	0.047	0.064	0.107	0.315	0.284	0.016	0.001
ETN+	0.273	0.291	0.163	0.103	0.063	0.042	0.025	0.016	0.012	0.007	0.004	0.002	0.000	0.000	0.000	0.000
ETN	0.037	0.078	0.121	0.110	0.103	0.092	0.083	0.075	0.068	0.064	0.064	0.075	0.026	0.004	0.000	0.000
Gol+	0.068	0.099	0.111	0.104	0.098	0.093	0.078	0.070	0.064	0.056	0.057	0.052	0.035	0.014	0.000	0.000
IFX+	0.004	0.015	0.030	0.051	0.070	0.092	0.108	0.115	0.119	0.121	0.114	0.099	0.050	0.013	0.000	0.000
PBO	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.029	0.970
TCZ+	0.032	0.094	0.156	0.173	0.159	0.125	0.092	0.062	0.045	0.031	0.018	0.010	0.004	0.000	0.000	0.000
TCZ	0.031	0.081	0.137	0.167	0.157	0.128	0.097	0.071	0.048	0.037	0.024	0.016	0.005	0.000	0.000	0.000
CTZ+	0.517	0.247	0.116	0.059	0.030	0.017	0.007	0.003	0.002	0.001	0.001	0.000	0.000	0.000	0.000	0.000
ABA sc+	0.021	0.041	0.058	0.066	0.077	0.085	0.091	0.097	0.093	0.094	0.096	0.093	0.064	0.024	0.000	0.000
TOF 5mg	0.001	0.004	0.010	0.022	0.029	0.045	0.062	0.080	0.102	0.122	0.149	0.185	0.140	0.048	0.000	0.000
TOF 10mg	0.012	0.037	0.063	0.081	0.100	0.114	0.118	0.112	0.102	0.090	0.083	0.055	0.026	0.007	0.000	0.000

Table 53: ACR (Main Trials plus Prior Biologics with AMBITION) – Probability of achieving at least ACR20

	Mean	SD	Median	95% CrI
cDMARDs	0.2811	0.0193	0.2809	0.2445, 0.3202
ABT iv+	0.5585	0.0563	0.5587	0.4471, 0.6684
ADA+	0.5695	0.0463	0.5694	0.4792, 0.6607
ADA	0.4318	0.0944	0.4291	0.2524, 0.6229
Int cDMARDs	0.4756	0.0959	0.4741	0.2906, 0.6662
ETN+	0.6889	0.0605	0.6913	0.5630, 0.7993
ETN	0.6132	0.0799	0.6160	0.4489, 0.7623
Gol+	0.6184	0.0769	0.6209	0.4616, 0.7618
IFX+	0.5754	0.0581	0.5758	0.4605, 0.6892
PBO	0.1500	0.0614	0.1420	0.0546, 0.2923
TCZ+	0.6358	0.0510	0.6367	0.5326, 0.7325
TCZ	0.6314	0.0545	0.6324	0.5206, 0.7357
CTZ+	0.7161	0.0471	0.7179	0.6187, 0.8035
ABA sc+	0.5819	0.0751	0.5827	0.4292, 0.7250
TOF 5mg	0.5425	0.0625	0.5432	0.4180, 0.6637
TOF 10mg	0.5938	0.0614	0.5951	0.4712 ,0.7109

Table 54: ACR (Main Trials plus Prior Biologics with AMBITION) – Probability of achieving at least ACR50

	Mean	SD	Median	95% CrI
cDMARDs	0.1189	0.0120	0.1184	0.0966, 0.1435
ABT iv+	0.3266	0.0519	0.3247	0.2307, 0.4344
ADA+	0.3362	0.0436	0.3345	0.2558, 0.4267
ADA	0.2247	0.0729	0.2175	0.1023, 0.3872
Int cDMARDs	0.2592	0.0787	0.2523	0.1241, 0.4313
ETN+	0.4598	0.0681	0.4588	0.3276, 0.5934
ETN	0.3815	0.0798	0.3792	0.2322, 0.5449
Gol+	0.3864	0.0774	0.3840	0.2418, 0.5446
IFX+	0.3425	0.0550	0.3404	0.2406, 0.4567
PBO	0.0528	0.0292	0.0471	0.0137, 0.1259
TCZ+	0.4015	0.0530	0.4002	0.3003, 0.5084
TCZ	0.3972	0.0563	0.3957	0.2898, 0.5121
CTZ+	0.4899	0.0558	0.4898	0.3813, 0.5998
ABA sc+	0.3503	0.0717	0.3470	0.2177, 0.4979
TOF 5mg	0.3128	0.0562	0.3108	0.2083, 0.4289
TOF 10mg	0.3604	0.0596	0.3587	0.2490, 0.4818

Table 55: ACR (Main Trials plus Prior Biologics with AMBITION) – Probability of achieving at least ACR70

	Mean	SD	Median	95% CrI
cDMARDs	0.0392	0.0052	0.0389	0.0298, 0.0502
ABT iv+	0.1529	0.0344	0.1501	0.0936, 0.2284
ADA+	0.1587	0.0292	0.1567	0.1076, 0.2218
ADA	0.0934	0.0416	0.0866	0.0322, 0.1923
Int cDMARDs	0.1133	0.0475	0.1060	0.0412, 0.2249
ETN+	0.2504	0.0548	0.2471	0.1523, 0.3655
ETN	0.1923	0.0577	0.1871	0.0948, 0.3194
Gol+	0.1956	0.0563	0.1906	0.0996, 0.3197
IFX+	0.1636	0.0373	0.1605	0.0994, 0.2456
PBO	0.0147	0.0105	0.0121	0.0027, 0.0421
TCZ+	0.2047	0.0392	0.2023	0.1346, 0.2881
TCZ	0.2018	0.0414	0.1991	0.1282, 0.2912
CTZ+	0.2741	0.0467	0.2722	0.1885, 0.3718
ABA sc+	0.1699	0.0495	0.1652	0.0868, 0.2803
TOF 5mg	0.1442	0.0363	0.1414	0.0822, 0.2239
TOF 10mg	0.1759	0.0414	0.1729	0.1042, 0.2656

5.3.2.6 ACR – Main Trials plus Prior Biologics without AMBITION

A network meta-analysis was used to compare the effects of abatacept iv +, MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo, tocilizumab (with and without MTX), certolizumab pegol + MTX, abatacept sc + and tofacitinib + MTX(5mg and 10mg doses) relative to cDMARDs on ACR response.

Data were available from 39 studies comparing two, three or four interventions.

Figure 10 presents the network of evidence and Table 56 presents the frequency with which each pair of treatments was compared. There were 15 treatment effects to estimate from 39 studies.

Figure 10: ACR (Main Trials plus Prior Biologics without AMBITION) – Network of evidence

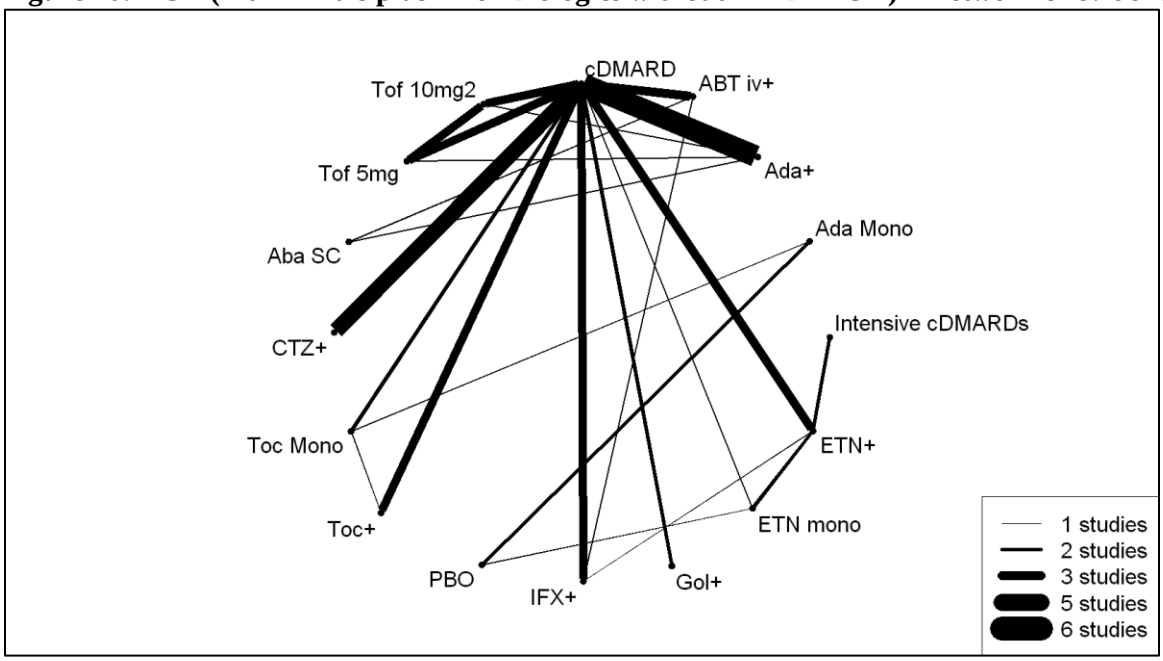


Table 56: ACR (Main Trials plus Prior Biologics without AMBITION) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ+	TCZ	CTZ+	ABA sc+	TOF 5mg	TOF 10mg
cDMARDs	-	3	6			3	1	2	3		3	2	5		3	3
ABT iv+	-	-							1					1		
ADA+	-	-	-											1	1	1
ADA	-	-	-	-						2		1				
Int cDMARDs	-	-	-	-	-	2										
ETN+	-	-	-	-	-	-	2		1							
ETN	-	-	-	-	-	-	-			1						
Gol+	-	-	-	-	-	-	-	-								
IFX+	-	-	-	-	-	-	-	-	-							
PBO	-	-	-	-	-	-	-	-	-	-						
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1				
TCZ	-	-	-	-	-	-	-	-	-	-	-	-				
CTZ+	-	-	-	-	-	-	-	-	-	-	-	-	-			
ABA sc+	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
TOF 5mg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
TOF 10mg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 57 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 58 presents the probabilities of treatment rankings.

There was some suggestion that model was not a good fit to all of the data, with the total residual deviance, 287.70, being larger than the total number of data points, 244, included in the analysis. However, the largest residual deviance, 34.9 (compared with 9 data points), was from the Kramer study and the deviance is likely to be a consequence of there being only one patient who had an ACR20 response and two patients who had an ACR50 response when treated with cDMARDS rather than a genuine lack of fit. The next largest residual deviances were 16.3 (compared with 6 data points) for the O'Dell study, 11.6 (compared with 6 data points) for the SATORI study, 11.0 (compared with 6 data points) for the ARMADA study and 10.2 (compared with 6 data points) for the JESMR study.

The between-study standard deviation was estimated to be 0.20 (95% CrI: 0.13, 0.31), which implies mild heterogeneity between studies in intervention effects. The exclusion of the AMBITION study had little impact on the estimate of the between study standard deviation.

All interventions except for placebo were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with certolizumab + MTX, etanercept + MTX and tocilizumab. The treatment effects were statistically significant for all interventions except for placebo at a conventional 5% level. Certolizumab + MTX (probability of being the best 0.450), etanercept + MTX (probability of being the best 0.256) and tocilizumab (probability of being the best 0.149) were the treatments that were most likely to be the most effective interventions. The exclusion of the AMBITION study has increased the treatment effects for adalimumab, tocilizumab (with and without MTX) back towards the effects estimated from the main studies alone but shrunk the effect of abatacept sc + MTX.

Table 57: ACR (Main Trials plus Prior Biologics without AMBITION) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.7289	0.1263	-0.7281	-0.9802, -0.4787
ADA+	-0.7535	0.1000	-0.7524	-0.9560, -0.5615
ADA	-0.4997	0.2395	-0.4997	-0.9661, -0.0286
Int cDMARDs	-0.5351	0.2344	-0.5358	-0.9946, -0.0737
ETN+	-1.0950	0.1593	-1.0950	-1.4090, -0.7843
ETN	-0.9019	0.1990	-0.9002	-1.2970, -0.5057
Gol+	-0.8881	0.1923	-0.8876	-1.2650, -0.5082
IFX+	-0.7723	0.1351	-0.7705	-1.0430, -0.5115
PBO	0.4190	0.2578	0.4172	-0.0845, 0.9303
TCZ+	-0.9663	0.1215	-0.9656	-1.2090, -0.7274
TCZ	-1.0480	0.1476	-1.0460	-1.3400, -0.7585
CTZ+	-1.1580	0.1229	-1.1600	-1.3980, -0.9127
ABA sc+	-0.7863	0.1783	-0.7863	-1.1380, -0.4296
TOF 5mg	-0.6860	0.1438	-0.6865	-0.9669, -0.3994
TOF 10mg	-0.8186	0.1450	-0.8199	-1.1020, -0.5338
Between study SD	0.2060	0.0464	0.2026	0.1250, 0.3072

Table 58, 59 and 60 present the probabilities of achieving at least an ACR20 response, at least an ACR50 response and at least an ACR70 response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 58: ACR (Main Trials plus Prior Biologics without AMBITION) – Probability of treatment rankings

	Rank															
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
cDMARDs	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.029	0.920	0.050
ABT iv+	0.000	0.002	0.007	0.016	0.030	0.055	0.083	0.111	0.131	0.148	0.156	0.145	0.085	0.031	0.000	0.000
ADA+	0.000	0.001	0.005	0.013	0.032	0.057	0.106	0.143	0.170	0.168	0.148	0.101	0.043	0.011	0.000	0.000
ADA	0.001	0.002	0.003	0.008	0.014	0.019	0.027	0.030	0.034	0.043	0.055	0.088	0.237	0.421	0.018	0.000
Int cDMARDs	0.000	0.003	0.006	0.011	0.016	0.024	0.032	0.037	0.042	0.048	0.065	0.101	0.257	0.347	0.012	0.000
ETN+	0.256	0.249	0.182	0.125	0.082	0.046	0.026	0.015	0.010	0.006	0.003	0.001	0.000	0.000	0.000	0.000
ETN	0.037	0.074	0.104	0.115	0.128	0.114	0.094	0.074	0.065	0.057	0.054	0.058	0.023	0.004	0.000	0.000
Gol+	0.052	0.078	0.089	0.100	0.109	0.111	0.095	0.076	0.066	0.060	0.057	0.054	0.037	0.017	0.000	0.000
IFX+	0.002	0.009	0.019	0.035	0.057	0.093	0.112	0.126	0.128	0.121	0.118	0.102	0.057	0.020	0.000	0.000
PBO	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.049	0.950
TCZ+	0.031	0.090	0.153	0.196	0.187	0.138	0.080	0.052	0.032	0.018	0.012	0.007	0.003	0.001	0.000	0.000
TCZ	0.149	0.197	0.203	0.170	0.112	0.068	0.039	0.025	0.015	0.010	0.007	0.003	0.001	0.000	0.000	0.000
CTZ+	0.450	0.244	0.143	0.082	0.044	0.021	0.009	0.004	0.002	0.001	0.001	0.000	0.000	0.000	0.000	0.000
ABA sc+	0.012	0.026	0.038	0.056	0.071	0.094	0.103	0.105	0.099	0.100	0.095	0.093	0.071	0.035	0.000	0.000
TOF 5mg	0.001	0.002	0.006	0.012	0.022	0.038	0.060	0.082	0.097	0.123	0.144	0.184	0.155	0.075	0.000	0.000
TOF 10mg	0.008	0.022	0.041	0.062	0.097	0.123	0.135	0.120	0.108	0.097	0.085	0.062	0.031	0.010	0.000	0.000

Table 59: ACR (Main Trials plus Prior Biologics without AMBITION) – Probability of achieving at least ACR20

	Mean	SD	Median	95% CrI
cDMARDs	0.2750	0.0186	0.2747	0.2393, 0.3124
ABT iv+	0.5514	0.0539	0.5516	0.4440, 0.6562
ADA+	0.5612	0.0445	0.5612	0.4739, 0.6497
ADA	0.4617	0.0942	0.4604	0.2810, 0.6488
Int cDMARDs	0.4754	0.0932	0.4752	0.2957, 0.6598
ETN+	0.6878	0.0588	0.6901	0.5667, 0.7961
ETN	0.6168	0.0771	0.6192	0.4580, 0.7617
Gol+	0.6118	0.0752	0.6135	0.4594, 0.7517
IFX+	0.5683	0.0568	0.5683	0.4553, 0.6797
PBO	0.1625	0.0635	0.1543	0.0621, 0.3084
TCZ+	0.6422	0.0496	0.6432	0.5409, 0.7376
TCZ	0.6713	0.0562	0.6728	0.5561, 0.7763
CTZ+	0.7103	0.0458	0.7124	0.6142, 0.7947
ABA sc+	0.5732	0.0719	0.5751	0.4274, 0.7109
TOF 5mg	0.5344	0.0605	0.5350	0.4133, 0.6509
TOF 10mg	0.5861	0.0599	0.5876	0.4659, 0.7009

Table 60: ACR (Main Trials plus Prior Biologics without AMBITION) – Probability of achieving at least ACR50

cDMARDs	0.1154	0.0115	0.1150	0.0940, 0.1391
ABT iv+	0.3202	0.0492	0.3183	0.2285, 0.4223
ADA+	0.3285	0.0413	0.3272	0.2516, 0.4145
ADA	0.2481	0.0759	0.2415	0.1183, 0.4147
Int cDMARDs	0.2589	0.0765	0.2533	0.1272, 0.4250
ETN+	0.4587	0.0662	0.4579	0.3317, 0.5892
ETN	0.3850	0.0775	0.3825	0.2393, 0.5445
Gol+	0.3797	0.0750	0.3774	0.2398, 0.5321
IFX+	0.3360	0.0533	0.3337	0.2369, 0.4471
PBO	0.0587	0.0312	0.0526	0.0161, 0.1350
TCZ+	0.4083	0.0521	0.4073	0.3091, 0.5144
TCZ	0.4400	0.0616	0.4388	0.3213, 0.5630
CTZ+	0.4832	0.0537	0.4834	0.3768, 0.5881
ABA sc+	0.3420	0.0676	0.3394	0.2158, 0.4826
TOF 5mg	0.3056	0.0537	0.3033	0.2050, 0.4159
TOF 10mg	0.3530	0.0576	0.3518	0.2450, 0.4711

Table 61: ACR (Main Trials plus Prior Biologics without AMBITION) – Probability of achieving at least ACR70

	Mean	SD	Median	95% CrI
cDMARDs	0.0373	0.0049	0.0371	0.0285, 0.0478
ABT iv+	0.1476	0.0320	0.1452	0.0921, 0.2177
ADA+	0.1526	0.0272	0.1506	0.1046, 0.2121
ADA	0.1058	0.0448	0.0990	0.0384, 0.2116
Int cDMARDs	0.1121	0.0459	0.1057	0.0425, 0.2197
ETN+	0.2480	0.0531	0.2449	0.1537, 0.3601
ETN	0.1934	0.0562	0.1884	0.0979, 0.3177
Gol+	0.1894	0.0538	0.1845	0.0985, 0.3073
IFX+	0.1580	0.0356	0.1551	0.0967, 0.2359
PBO	0.0165	0.0115	0.0137	0.0032, 0.0456
TCZ+	0.2084	0.0387	0.2060	0.1389, 0.2917
TCZ	0.2330	0.0480	0.2298	0.1469, 0.3349
CTZ+	0.2669	0.0444	0.2655	0.1847, 0.3587
ABA sc+	0.1630	0.0459	0.1589	0.0854, 0.2647
TOF 5mg	0.1386	0.0342	0.1358	0.0792, 0.2124
TOF 10mg	0.1697	0.0395	0.1670	0.1011, 0.2554

5.3.2.7 ACR – Main Trials plus RCTs that have potentially low prior MTX exposure

A network meta-analysis was used to compare the effects of abatacept iv +, MTX, adalimumab (with and without MTX), intensive cDMARDs, etanercept (with and without MTX), golimumab + MTX, infliximab + MTX, placebo, tocilizumab (with and without MTX), certolizumab pegol + MTX, abatacept sc + and tofacitinib + MTX (5mg and 10mg doses) relative to cDMARDs on ACR response.

Data were available from 30 studies comparing two or three interventions.

Figure 11 presents the network of evidence and Table 62 presents the frequency with which each pair of treatments was compared. There were 13 treatment effects to estimate from 30 studies.

Figure 11: ACR (Main Trials plus cDMARD Naive) – Network of evidence

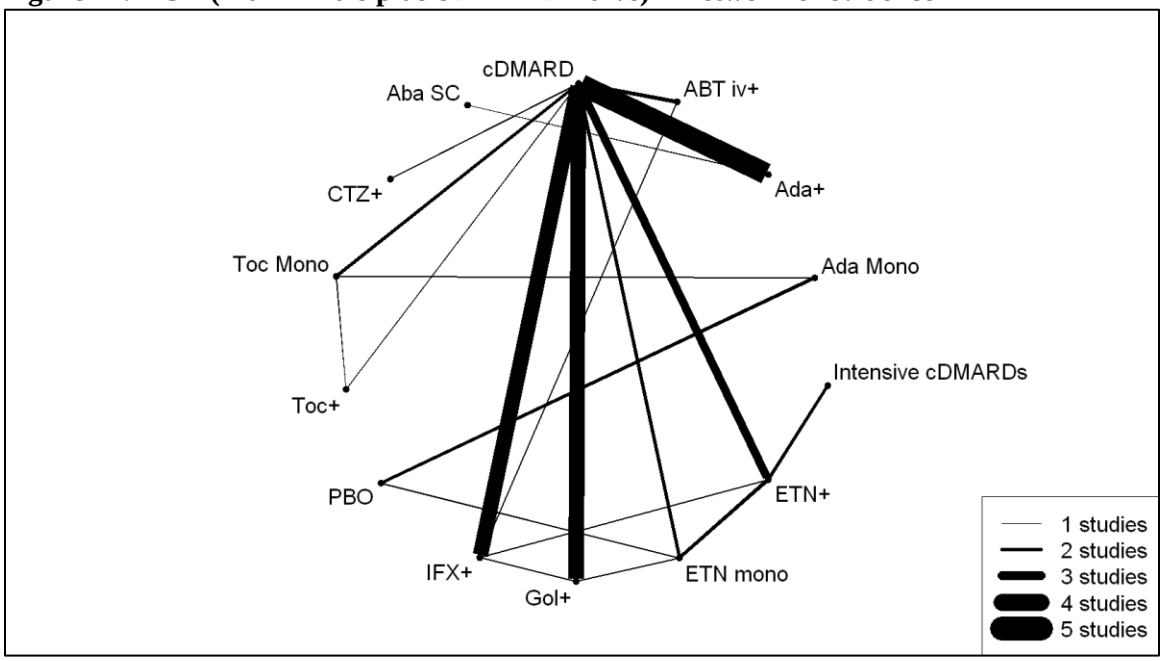


Table 62: ACR (Main Trials plus cDMARD Naive) – Frequency with which each pair of interventions were compared

Intervention	cDMARDs	ABT iv+	ADA+	ADA	Int cDMARDs	ETN+	ETN	Gol+	IFX+	PBO	TCZ+	TCZ	CTZ+	ABA SC+
cDMARDs	-	2	5		1	5	2	2	3		1	2	1	
ABT iv+	-	-							1					
ADA+	-	-	-											1
ADA	-	-	-	-						2		1		
Int cDMARDs	-	-	-	-	-	3								
ETN+	-	-	-	-	-	-	3		1					
ETN	-	-	-	-	-	-	-			1				
Gol+	-	-	-	-	-	-	-	-						
IFX+	-	-	-	-	-	-	-	-	-					
PBO	-	-	-	-	-	-	-	-	-	-				
TCZ+	-	-	-	-	-	-	-	-	-	-	-	1		
TCZ	-	-	-	-	-	-	-	-	-	-	-	-		
CTZ+	-	-	-	-	-	-	-	-	-	-	-	-	-	
ABA SC+	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 63 presents the effects of each intervention relative to cDMARDs on the probit scale and Table 64 presents the probabilities of treatment rankings.

The model fitted the data reasonably well, with the total residual deviance, 205.30, close to the total number of data points, 192, included in the analysis. The largest residual deviances were 15.3 (compared with 6 data points) for the O'Dell study, 12.0 (compared with 6 data points) for the SATORI study and 10.0 (compared with 6 data points) for the ARMADA study.

The between-study standard deviation was estimated to be 0.30 (95% CrI: 0.20, 0.46), which implies mild heterogeneity between studies in intervention effects. The addition of the TEAR and TEMPO studies has increased the variability between treatment effects relative to that estimated from the main studies alone.

All interventions except for PBO were associated with beneficial treatment effects relative to cDMARDs with the greatest effects being associated with tocilizumab (with and without MTX). The treatment effects were statistically significant for all interventions except for certolizumab pegol + MTX, adalimumab, Int cDMARDs and placebo at a conventional 5% level. Tocilizumab + MTX (probability of being the best 0.268), TCZ (probability of being the best 0.232), abatacept sc + MTX (probability of being the best 0.210) and Golimumab + MTX (probability of being the best 0.134) were the treatments that were most likely to be the most effective interventions.

Table 63: ACR (Main Trials plus cDMARD Naive) – Effects of interventions relative to cDMARDs on the probit scale

	Mean	SD	Median	95% CrI
ABT iv+	-0.7109	0.2282	-0.7113	-1.1590, -0.2576
ADA+	-0.8404	0.1593	-0.8377	-1.1590, -0.5310
ADA	-0.3563	0.3157	-0.3559	-0.9851, 0.2634
Int cDMARDs	-0.3955	0.2194	-0.3924	-0.8330, 0.0289
ETN+	-0.8329	0.1484	-0.8297	-1.1350, -0.5478
ETN	-0.5235	0.1963	-0.5210	-0.9154, -0.1398
Gol+	-0.8971	0.2519	-0.8961	-1.3990, -0.3959
IFX+	-0.7562	0.1815	-0.7538	-1.1210, -0.3972
PBO	0.6463	0.3240	0.6462	0.0059, 1.2780
TCZ+	-1.0390	0.2498	-1.0400	-1.5360 ,-0.5417
TCZ	-1.0440	0.2086	-1.0430	-1.4590, -0.6324
CTZ+	-0.6433	0.3700	-0.6419	-1.3710, 0.0917
ABA SC+	-0.8979	0.3652	-0.8965	-1.6160, -0.1747
Between study SD	0.3084	0.0655	0.3007	0.2015, 0.4568

Table 64: ACR (Main Trials plus cDMARD Naive) – Probability of treatment rankings

	Rank													
Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14
cDMARDs	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.016	0.173	0.788	0.021
ABT iv+	0.024	0.042	0.058	0.075	0.090	0.106	0.128	0.144	0.132	0.100	0.067	0.032	0.002	0.000
ADA+	0.021	0.068	0.114	0.164	0.167	0.157	0.129	0.092	0.054	0.023	0.008	0.002	0.000	0.000
ADA	0.003	0.005	0.010	0.016	0.021	0.027	0.036	0.056	0.085	0.130	0.200	0.292	0.117	0.000
Int cDMARDs	0.000	0.001	0.002	0.005	0.011	0.020	0.030	0.058	0.105	0.193	0.279	0.267	0.028	0.002
ETN+	0.023	0.061	0.107	0.151	0.172	0.171	0.148	0.103	0.052	0.010	0.001	0.000	0.000	0.000
ETN	0.001	0.003	0.006	0.014	0.025	0.041	0.068	0.114	0.191	0.259	0.203	0.072	0.002	0.000
Gol+	0.134	0.126	0.138	0.117	0.102	0.094	0.084	0.073	0.059	0.038	0.024	0.009	0.000	0.000
IFX+	0.017	0.038	0.067	0.096	0.121	0.141	0.157	0.149	0.112	0.063	0.031	0.009	0.000	0.000
PBO	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.005	0.022	0.971
TCZ+	0.268	0.225	0.153	0.101	0.076	0.057	0.044	0.033	0.022	0.012	0.006	0.003	0.000	0.000
TCZ	0.232	0.267	0.181	0.111	0.078	0.051	0.038	0.023	0.013	0.005	0.001	0.000	0.000	0.000
CTZ+	0.067	0.053	0.059	0.061	0.060	0.063	0.072	0.085	0.111	0.111	0.115	0.106	0.033	0.004
ABA SC+	0.210	0.111	0.102	0.089	0.077	0.071	0.066	0.070	0.065	0.054	0.047	0.031	0.007	0.001

Table 65, 66 and 67 present the probabilities of achieving at least an ACR20 response, at least an ACR50 response and at least an ACR70 response, respectively. These are derived by combining the treatment effects estimated from the network meta-analysis with the estimate of the cDMARDs "No response" rate.

Table 65: ACR (Main Trials plus cDMARD Naive) – Probability of achieving at least ACR20

	Mean	SD	Median	95% CrI
cDMARDs	0.3260	0.0325	0.3252	0.2641, 0.3916
ABT iv+	0.5989	0.0921	0.6021	0.4096, 0.7697
ADA+	0.6484	0.0671	0.6506	0.5096, 0.7741
ADA	0.4634	0.1238	0.4619	0.2295, 0.7105
Int cDMARDs	0.4776	0.0917	0.4759	0.3010, 0.6610
ETN+	0.6459	0.0635	0.6468	0.5186, 0.7665
ETN	0.5275	0.0840	0.5280	0.3609, 0.6929
Gol+	0.6660	0.0945	0.6714	0.4655, 0.8353
IFX+	0.6169	0.0759	0.6188	0.4633, 0.7591
PBO	0.1487	0.0763	0.1356	0.0390, 0.3340
TCZ+	0.7146	0.0875	0.7209	0.5228, 0.8671
TCZ	0.7178	0.0754	0.7224	0.5563, 0.8512
CTZ+	0.5707	0.1397	0.5753	0.2853, 0.8266
ABA sc+	0.6615	0.1288	0.6711	0.3828 0.8820

Table 66: ACR (Main Trials plus cDMARD Naive) – Probability of achieving at least ACR50

	Mean	SD	Median	95% CrI
cDMARDs	0.1395	0.0207	0.1384	0.1022, 0.1834
ABT iv+	0.3575	0.0892	0.3540	0.1928, 0.5420
ADA+	0.4042	0.0704	0.4022	0.2708, 0.5483
ADA	0.2438	0.0994	0.2326	0.0847, 0.4687
Int cDMARDs	0.2505	0.0745	0.2433	0.1237, 0.4143
ETN+	0.4011	0.0667	0.3984	0.2774, 0.5381
ETN	0.2909	0.0732	0.2863	0.1607, 0.4496
Gol+	0.4272	0.1020	0.4249	0.2345, 0.6335
IFX+	0.3729	0.0757	0.3703	0.2333, 0.5286
PBO	0.0503	0.0360	0.0413	0.0082, 0.1441
TCZ+	0.4816	0.1021	0.4805	0.2807, 0.6851
TCZ	0.4833	0.0889	0.4826	0.3112, 0.6583
CTZ+	0.3392	0.1309	0.3284	0.1142, 0.6205
ABA sc+	0.4296	0.1379	0.4244	0.1756, 0.7096

Table 67: ACR (Main Trials plus cDMARD Naive) – Probability of achieving at least ACR70

	Mean	SD	Median	95% CrI
cDMARDs	0.0475	0.0093	0.0468	0.0315, 0.0680
ABT iv+	0.1742	0.0623	0.1676	0.0731, 0.3150
ADA+	0.2054	0.0521	0.2012	0.1152, 0.3195
ADA	0.1049	0.0597	0.0936	0.0247, 0.2511
Int cDMARDs	0.1063	0.0440	0.0993	0.0402, 0.2102
ETN+	0.2029	0.0493	0.1986	0.1188, 0.3101
ETN	0.1299	0.0459	0.1242	0.0570, 0.2368
Gol+	0.2258	0.0791	0.2179	0.0945, 0.4014
IFX+	0.1836	0.0537	0.1784	0.0939, 0.3028
PBO	0.0139	0.0133	0.0101	0.0014, 0.0494
TCZ+	0.2690	0.0854	0.2615	0.1212, 0.4559
TCZ	0.2688	0.0740	0.2632	0.1391, 0.4288
CTZ+	0.1671	0.0919	0.1509	0.0363, 0.3872
ABA sc+	0.2329	0.1097	0.2174	0.0643, 0.4846

5.4 Discussion of systematic reviewing results

This review differed from other reviews of biologics in RA, in that it only included licensed doses of biologics, was limited to first line biologics, and considered separately methotrexate-naive and cDMARD experienced trials.

Sixty trials met the inclusion criteria for the systematic review of clinical effectiveness and safety evidence. Of these, 37 trials were also used in the NMA (7 for population 1 and 30 population for 2). Seven MTX-naïve trials and 24 c-DMARD-experienced trials (of which 4 were head-to-head evidence) were included in the NMA for ACR response. One MTX-naive trial and ten cDMARD experienced trials were included in the review and in the NMA for EULAR data.

In addition, 14 trials (12 trials with interventions of interest and 2 tofacitinib trials) were included in sensitivity analyses (14 with ACR data and four with EULAR data).

Many of the trials were of good quality. They were mostly phase III trials (some phase II or IIII). Some trials did not report in enough detail to judge randomisation method or allocation concealment, or whether all outcomes were reported.

There were several large, multinational, multicentre studies. A few trials were conducted in a single country. For the cDMARD experienced population, some trial populations may not have had adequate

MTX to class as failure. Of particular note, for Population 2/3, are the trials that were conducted in Japan only, as some of these trials also utilised low dose MTX treatment prior to randomisation, potentially impacting on the extent of MTX failure among trial populations and restricting external validity to the UK.

The issues relating to the external validity of RCTs in RA including i) the application of strict trial inclusion criteria resulting in narrower study populations relative to RA clinical practice and ii) the limitations of RCTs in general in capturing rare adverse events, have been previously discussed and should be borne in mind when considering the generalisability of the trial evidence.[147,148] Some trials had step-up therapy, which is consistent with real world practice.

Strengths of this systematic review included: the undertaking of a comprehensive search for evidence; the extensive number of RCTs that were identified relating to the decision problem; data were identified for all interventions of interest; there were long-term safety data from long-term extensions of trials; trials that were not eligible for inclusion in the systematic review or NMA base case (e.g. trials with populations having ≤ 20% prior biologic experience) were explored in sensitivity analyses; and graphical data for the NMA were extracted using software.

Limitations of the review included: evidence was restricted to English language publications; ongoing/unpublished trial resources could not be explored due to the timescales of the assessment; and, due to the extensive variability in the range of available outcome measures reported in trials it was necessary to prioritise the assessment of the most widely used measures.

Whilst there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in Population 1, infliximab + MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups; Intensive cDMARDs + prednisolone and adalimumab + MTX; etanercept, golimumab + MTX and step-up combination cDMARDs; adalimumab and cDMARDs.

Whilst there was uncertainty in, and overlap between the effects of treatment on EULAR for interventions in Population 2 and 3 in the main trials, etanercept + MTX and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: tocilizumab, golimumab + MTX, adalimumab + MTX, abatacept iv + MTX and grouped biologics; etanercept, infliximab + MTX, adalimumab and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly

the same groupings, although certolizumab pegol + MTX was associated with an even bigger response than etanercept + MTX and tocilizumab + MTX.

Whilst there was uncertainty in, and overlap between the effects of treatment on ACR for interventions in Population 2 and 3 in the main trials, etanercept + MTX, tocilizumab and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups:,etanercept, golimumab + MTX, abatacept sc + MTX, adalimumab + MTX, infliximab + MTX and abatacept iv + MTX; certolizumab pegol + MTX, intensive cDMARDs and adalimumab. The inclusion of the additional studies in which patients received prior biologics suggested that certolizumab pegol + MTX and etanercept + MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and adalimumab which are associated with even smaller response rates.

5.4.1 Other efficacy outcomes

Population 1 MTX-naive

Where there was step-up therapy with initial biologic or control, the groups were similar after six months to a year (i.e. after step-up). Biologic monotherapy was better than PBO, but similar to MTX. Biologic combined with MTX was better than MTX+PBO.

Population 2/3 cDMARD experienced

Head-to-head trials indicate similarity of biologics. One exception was the ADACTA trial.

This reported greater improvement with TCZ monotherapy than ADA monotherapy for DAS and MCS of SF-36 at 24 weeks (ADACTA) although this trial had similar results for ADA and TCZ for swollen and tender joint counts, and fatigue. This suggests that the impacts of different biologics on different outcomes may not be straightforward.

Biologics combined with MTX treatment arms reported more improvement than non-biologic control arms with one or two cDMARDs or baseline cDMARDs. Biologics combined with MTX did better than biologic monotherapy, except for TCZ for joint counts and HAQ-DI.

6. ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

The Assessment Group conducted a systematic review of published economic evaluations undertaken of the RA interventions being assessed. The objective of this systematic review is to summarise the existing economic evidence for the use of each intervention in patients with RA. The systematic review will assess the strengths and limitations of each specific economic evaluation.

6.1.1 Methods for reviewing existing cost-effectiveness evidence

Systematic searches of online databases were undertaken to identify all published economic evaluations of disease modifying therapies for rheumatoid arthritis. To ensure that the systematic search had high sensitivity, the search was developed by applying economic terms to a general disease search for rheumatoid arthritis and disease modifying therapies. Database filters to identify economic evaluations were used from the InterTASC Information Specialists' Sub-Group (ISSG) website[*].

Table 68: Keywords for systematic review

Population	**Rheumatoid Arthritis, RA**
Intervention/Comparator	Disease modifying, disease-modifying, DMARD, biologic, therapy, treatment, anti-rheumatic, anti rheumatic, TNF, tumor necrosis factor alpha, tumour necrosis factor alpha, TNF-alpha, TNF inhibitor, TNF blocker, interleukin 1, IL-1, monoclonal antibody, costimulation blocker, interleukin 6, IL-6
Outcomes	Economic, economics, cost, cost-effectiveness, cost-utility, cost-benefit, utility, health related quality of life, quality of life, quality adjusted life year, QALY

The search strategies used MeSH terms, including 'rheumatoid arthritis' and 'economics' and text string terms which were combined in the search strategy using Boolean logic. The search strategies were designed to maximise sensitivity (i.e. the identification of all appropriate studies) however this was at the cost of poor specificity (the rejection of inappropriate studies). This meant the search returned a lot of inappropriate studies and was reliant on hand sifting, including the removal of economic evaluations of treatments that are not included in this appraisal (rituximab, conventional DMARDs, anakinra etc).

Systematic searches were conducted in ten databases. Conference abstracts were not included, however authors were hand searched to identify any later publications. Reference search was undertaken on all included studies, including any identified reviews of published economic evaluations of disease modifying therapies for rheumatoid arthritis.

[*] www.york.ac.uk/inst/crd/intertasc/index.htm

Table 69: Systematic review databases

Database	Date
BIOSIS (all databases)	1899 – Feb 2013
Cochrane Database of Systematic Reviews (CDSR)	All years – Feb 2013
Cochrane Database of Methodological Reviews	All years – Feb 2013
Cochrane Central Register of Controlled Trials (CCRCT)	All years – Feb 2013
Database of Abstracts of Reviews and Effects (DARE)	All years – Feb 2013
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	1994 – Feb 2013
Embase	1974 – Feb 2013
MEDLINE	1945 – Feb 2013
NHS Economic Evaluations Database (NHSEED)	All years – Feb 2013
Science Citation Index: Web of Science	1899 – Feb 2013

All database searches were undertaken on 1st February 2013, and no date restriction was applied. No study type or language restrictions were applied to the electronic search. The search strategies were reviewed by an information specialist.

The objective of the systematic search was to identify economic evaluations of abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab within Populations 1, 2 and 3. The search was irrespective of the decision-making context or the geographical location. The eligibility criteria are presented in Table 70.

Table 70: Eligibility Criteria

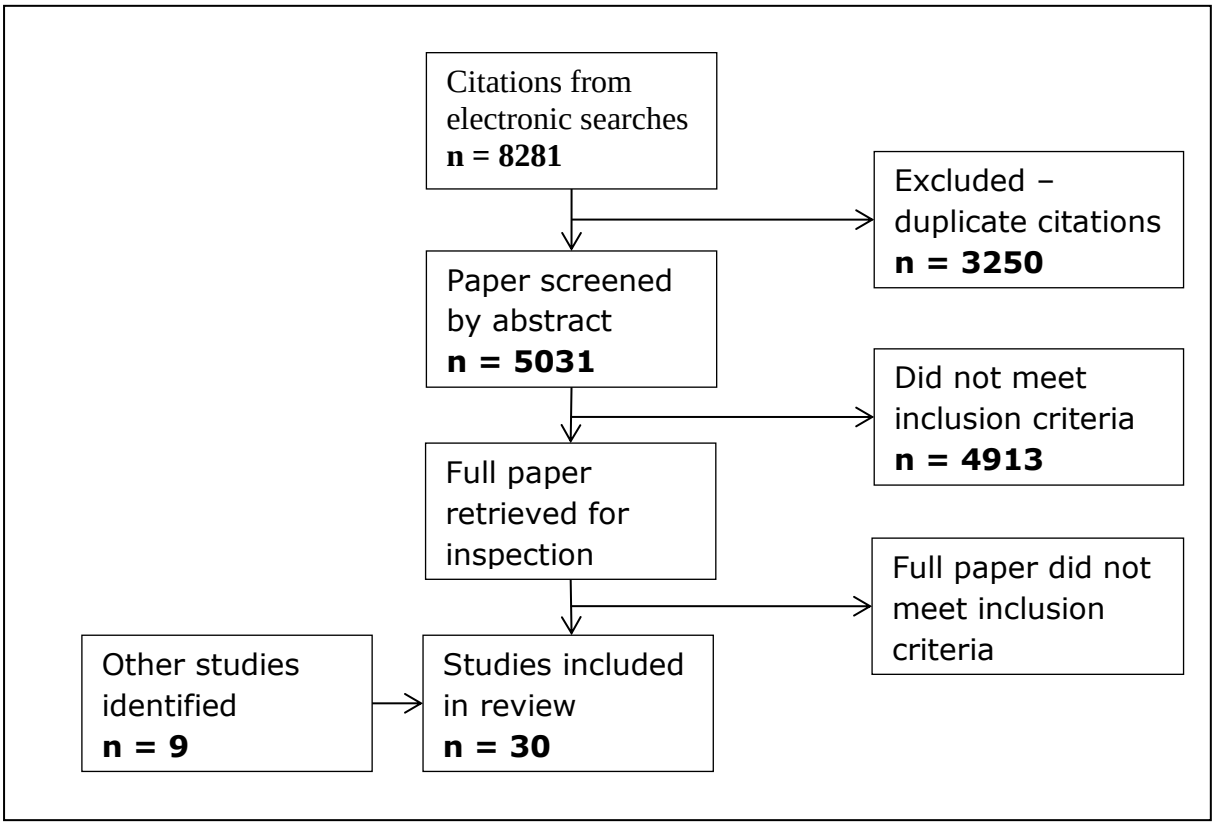
Inclusion Criteria
• Economic evaluation including a comparison of costs and benefits based on outcomes data or undertaken using decision-analytic methods • Economic evaluations of interventions targeting a change to the natural disease profile of people with rheumatoid arthritis (i.e. disease-modifying therapies) • Studies reporting costs and health outcomes
Exclusion Criteria
• Evaluations of treatments not under review in this appraisal • Evaluations in patient populations not under review in this appraisal (e.g. sequential biologics) • Partial or non-comparative economic evaluations • Cost analyses/Cost-of-illness/Burden-of-illness studies • Methodological papers which do not report economic and health benefit outcomes • Commentaries, letters, editorials • Conference abstracts • Studies which claim cost-effectiveness but with no empirical estimation of the costs and effectiveness outcomes • Economic evaluations of therapies and treatments which do not modify the natural progression of rheumatoid arthritis • Non-English language

The identified studies were appraised using the commonly used and validated Drummond 'Critical appraisal of a published article' checklist[149].

6.1.2 Results

From the systematic searching of electronic databases, 8,281 citations were identified (QUOROM flow-diagram provided in Figure 12). After excluding 3,250 duplicate citations electronically, the remaining 5,031 citations were screened by their abstract. Of these, 4,913 abstracts did not meet the inclusion criteria and 118 full papers were retrieved for a full inspection. A total of 97 papers were excluded for not meeting the inclusion criteria, and 9 other studies were identified by reference searches and searching any identified systematic reviews. 30 studies were included in the systematic review.

Figure 12: QUOROM flow diagram



The studies identified are summarised in Table 71. 23 of the 30 studies (77%) were evaluations of bDMARDs in patients who had already had DMARD therapy previously. 6 studies (20%) were in DMARD naïve patients, with one study (3%) in both DMARD naïve and experienced populations.

No studies were identified that evaluated golimumab and certolizumab pegol, with the majority focussing on the established TNFa's (etanercept, infliximab and adalimumab).

27 of the 30 studies (90%) were CUA's, and a wide range of model methods and time horizons were adopted.

Table 71: Health economic studies assessing bDMARDs in bDMARD naïve patients with RA

Study	Treatment history	Disease severity	Country (sponsor)	Interventions considered	Form of economic analysis	Model used	Time Horizon
Bansback *et al.* 2005[150]	2 cDMARDs	Moderate / Severe	Sweden (Abbott)	TNFa with or without MTX vs. cDMARDs	CUA	Individual level Markov model	Lifetime
Barbieri *et al.* 2005[151]	cDMARDs and resistant to MTX	Severe	UK (Schering-Plough)	IFX+MTX vs. MTX	CUA	Markov model	1 year and lifetime
Barton *et al.* 2004[152]	SSZ and MTX	Unclear	UK (HTA)	ETN vs. IFX vs. cDMARD sequence	CUA	Individual Sampling Model	Lifetime
Benucci *et al.* 2009[153]	2 cDMARDs	Moderate / Severe	Italy (None reported)	ABT with LEF or MTX vs. ETN with LEF or MTX	CUA	Observational analysis	2 years
Brennan *et al.* 2004[154]	2 cDMARDs	Unclear	UK (Wyeth)	ETN vs. cDMARD sequence	CUA	Individual Sampling Model	Lifetime
Brennan *et al.* 2007[155]	At least 2 cDMARDs	Active	UK (BSRBR)	TNFa vs. cDMARDs	CUA	Individual Sampling Model	Lifetime
Chen *et al.* 2006[113]	None (at least for first line comparators)	Active	UK (HTA)	TNFa with or without MTX at first line or third line	CUA	Individual Sampling Model	Lifetime
Chiou *et al.* 2004[156]	Unclear	Moderate / Severe	US (None reported)	ANA vs. ETN vs. ADA vs. IFX	CUA	Decision tree	1 year
Choi *et al.* 2002[157]	MTX	Unclear	US (No funding	cDMARD mono and combo vs.	CEA	Decision tree	6

Study	Treatment history	Disease severity	Country (sponsor)	Interventions considered	Form of economic analysis	Model used	Time Horizon
			source)	bDMARD mono and combo			months
Coyle *et al.* 2006[158]	None	Aggressive	Canada (CCOHTA)	GLD vs. bDMARD mono and combo	CUA	Markov model	5 years
Davies *et al.* 2009[159]	None	Unclear	US (Abbott)	MTX vs. ADA+MTX vs. ETN vs. IFX+MTX vs. ADA+MTX	CUA	Individual Sampling Model	Lifetime
Diamantopoulos *et al.* 2012[160]	cDMARDs	Moderate / Severe	Italy (Roche)	Sequential bDMARD use	CUA	Individual Sampling Model	lifetime
Finckh *et al.* 2009[161]	None	Active	US (Arthritis Foundation)	Symptomatic therapy vs. MTX vs. bDMARDs	CUA	Individual Sampling Model	Lifetime
Jobanputra *et al.* 2002[162]	SSZ and MTX	Active	UK (HTA)	Adding ETN and IFX into a cDMARD sequence	CUA	Individual Sampling Model	Lifetime
Kobelt *et al.* 2003[163]	cDMARDS including MTX IR	Unclear, "advanced"	Sweden, UK (Schering-Plough)	IFX+MTX vs. MTX	CUA	Markov model	10 year
Kobelt *et al.* 2004[164]	2 cDMARDS including MTX IR	Unclear	Sweden (multiple funders)	TNFa vs. cDMARDs	CUA	Trial analysis	1 year
Kobelt *et al.* 2005[165]	cDMARDs other than MTX	Severe	Sweden (Wyeth)	ETN vs. MTX vs. ETN+MTX	CUA	Markov model	5 year/ 10 year
Kobelt *et al.* 2011[166]	None	Severe	Sweden (Wyeth)	ETN+MTX vs. MTX	CUA	Markov model	10 year

Study	Treatment history	Disease severity	Country (sponsor)	Interventions considered	Form of economic analysis	Model used	Time Horizon
Lekander *et al.* 2010[167]	no aTNFs	Active	Sweden (Schering-Plough)	IFX vs. cDMARDs	CUA	Markov model	20 year
Marra *et al.* 2007[168]	cDMARDs	Active	Canada (None reported)	IFX+MTX vs. MTX	CUA	Markov model	10 years
Nuijten *et al.* 2001[169]	2 cDMARDs	Unclear	Netherlands (Wyeth)	ETN vs. IFX	CMA	Unclear	1 year
Rubio-Terrés *et al.* 2001[170]	cDMARDs (inc MTX)	Active	Spain (None reported)	IFX+MTX vs. LEF	CMA	Unclear	1 year
Soini *et al.* 2012[171]	At least 1 cDMARD	Moderate / Severe	Finland (Roche)	ADA vs. ETN vs. TCZ	CUA	Individual Sampling Model	Lifetime
Spalding *et al.* 2006[172]	None	Unclear	US (University of Southern California)	MTX vs. bDMARD mono and combos	CUA	Markov model	Lifetime
Tanno *et al.* 2006[173]	Bucillamine	Unclear	Japan (Japanese Government)	Adding ETN to a cDMARD sequence	CUA	Markov model	Lifetime
van den Hout *et al.* 2009[174]	None	Active	Netherlands (multiple funders)	Comparing cDMARD combos vs. IFX combo therapy	CUA	Trial analysis	2 year
Vera-Llonch *et al.* 2008[175]	MTX	Moderate / Severe	US (None reported)	ABT vs. cDMARDs	CUA	Individual Sampling Model	Lifetime
Wailoo *et al.* 2008[176]	No bDMARDs	Unclear	US (US AHRQ)	ETN vs. ADA vs. ANA vs. IFX	CUA	Individual Sampling Model	Lifetime

Study	Treatment history	Disease severity	Country (sponsor)	Interventions considered	Form of economic analysis	Model used	Time Horizon
Welsing *et al.* 2004[177]	cDMARDs	Active	Netherlands (None reported)	Usual care vs. LEF vs. TNFa vs. LEF,TNFa sequences	CUA	Markov model	5 years
Wong *et al.* 2002[178]	MTX	Active refractory disease	US (Schering-Plough, NIH)	IFX+MTX vs. MTX	CUA	Markov model	Lifetime

For ease of viewing, the cost-effectiveness results are split into cDMARD naïve (Table 72) and bDMARD naive (Table 73) populations.

The range of price year, currencies, discount rates and time horizons mean that drawing strong conclusions regarding the cost-effectiveness of particular therapies is not possible, and would likely be misleading. Also, the complex nature of RA and the range of parameters required to develop a cost-effectiveness model mean that a very detailed review of each study would be required, which was not feasible. In some instances, the price year was not reported, and in a few cases it was not clear if bDMARDs were given with concomitant MTX or if they were a monotherapy. Results in GBP £ are all above the £30k per QALY threshold.

In general, the results in Table 73 suggest that bDMARDs are unlikely to be cost-effective in patients who have not undertaken DMARD therapy.

Table 72: Cost-effectiveness results for studies in DMARD naïve patients with RA

Drug	Comparator	Study	Price Year	Time horizon	Previous treatments	ICER (per QALY gained)
ADA	MTX	Spalding *et al.* 2006[172]	2005	Lifetime	None	$64k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	None	£53k
ADA + MTX	MTX	Spalding *et al.* 2006[172]	2005	Lifetime	None	$195k
	cDMARDs	Davies *et al.* 2009[159]	2007	Lifetime	None	$23k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	None	£170k
ETN	MTX	Spalding *et al.* 2006[172]	2005	Lifetime	None	$90k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	None	£49k
	cDMARDs	Davies *et al.* 2009[159]	2007	Lifetime	None	$28k
ETN + MTX	MTX	Kobelt *et al.* 2011[166]	2008	10 year	None	Euro 14k
	cDMARDs	Coyle *et al.* 2006[158]	?	5 years	None	Before/After Gold = Can$145k/Can$126k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	None	£78k
IFX + MTX	MTX	Spalding *et al.* 2006[172]	2005	Lifetime	None	$410k
	cDMARDs	Coyle *et al.* 2006[158]	?	5 years	None	Before/After Gold = Can$113k/Can$98k
	cDMARDs	Davies *et al.* 2009[159]	2007	Lifetime	None	$32k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	None	£650k
	Combination cDMARDs	van den Hout *et al.* 2009[174]	2008	2 year	None	Euro 130k
TNFa	cDMARDs	Finckh *et al.* 2009[161]	2007	Lifetime	None	Dominated

Like the DMARD naïve population, it is not possible to provide conclusions regarding the cost-effectiveness of individual treatments in the bDMARD naive population.

Many bDMARDs have ICERs close to £30k per QALY threshold. No one bDMARD consistently seems to be cost effective compared to any other bDMARD.

Jobanputra *et al.* 2002[162], Barton *et al.* 2004[152] and Chen *et al.* 2006[113] are HTA reports which informed the development of NICE TA36 and TA130. Taking the most recent HTA report by Chen *et al.* 2006[113], ADA, ADA+MTX, ETN, ETN+MTX and IFX+MTX all have ICERs compared to cDMARDs exceeding £20k per QALY, and in many instances above £30k per QALY. However these drugs have since been recommended in certain patient populations. This highlights the sensitivity of cost-effectiveness models to key parameters and modelling assumptions, and careful consideration of all aspects is required to ensure confidence in the final reported ICERs.

Table 73: Cost-effectiveness results for studies in bDMARD naïve patients with RA

Drug	Comparator	Study	Price Year	Time horizon	Previous treatments	ICER (per QALY gained)
ABA + MTX	MTX	Vera-Llonch *et al.* 2008[175]	2006	Lifetime	MTX	$46k
ADA	MTX	Bansback *et al.* 2005[150]	2001	Lifetime	2 previous cDMARDs	Euro 42k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	2 previous cDMARDs	£35-140k
	Anakinra	Chiou *et al.* 2004[156]	2003	1 year	Unclear	Dominated
	Anakinra	Wailoo *et al.* 2008[176]	?	Lifetime	No bDMARDs	$143k
	IFX + MTX	Wailoo *et al.* 2008[176]	?	Lifetime	No bDMARDs	Dominates
ADA + MTX	MTX	Bansback *et al.* 2005[150]	2001	Lifetime	2 previous cDMARDs	Euro 34k
	MTX	Soini *et al.* 2012[171]	2010	Lifetime	At least 1 cDMARD	Euro 21k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	2 previous cDMARDs	£30-64k
	Anakinra	Chiou *et al.* 2004[156]	2003	1 year	Unclear	Dominated
ETN	MTX	Bansback *et al.* 2005[150]	2001	Lifetime	2 previous cDMARDs	Euro 37k
	MTX	Tanno *et al.* 2006[173]	2005	Lifetime	Bucillamine	Yen 2.5million
	MTX	Kobelt *et al.* 2005[165]	2004	5 years / 10 years	cDMARDs other than MTX	5 year / 10 year = Euro 152k / 124k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	2 previous cDMARDs	£24-47k
	Anakinra	Chiou *et al.* 2004[156]	2003	1 year	Unclear	$13k
	IFX + MTX	Nuijten *et al.* 2001[169]	1999	1 year	2 cDMARDs	Dominates

Drug	Comparator	Study	Price Year	Time horizon	Previous treatments	ICER (per QALY gained)
	ETN + MTX and cDMARD strategies	Choi *et al.* 2002[157]	1999	6 months	MTX	Extendedly dominated
ETN + MTX	MTX	Bansback *et al.* 2005[150]	2001	Lifetime	2 previous cDMARDs	Euro 36k
	MTX	Soini *et al.* 2012[171]	2010	Lifetime	At least 1 cDMARD	Euro 21k
	MTX	Kobelt *et al.* 2005[165]	2004	5 year / 10 year	cDMARDs other than MTX	5 year / 10 year = Euro 55k / 37k
	cDMARDs	Barton *et al.* 2004[152]	2000	Lifetime	SSZ and MTX	£50k
	cDMARDs	Brennan *et al.* 2004[154]	2000	Lifetime	2 cDMARDs	£16k
	cDMARDs	Jobanputra *et al.* 2002[162]	2000	Lifetime	SSZ and MTX	£64k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	2 previous cDMARDs	£24-50k
	Anakinra	Chiou *et al.* 2004[156]	2003	1 year	Unclear	$8k
	ADA + MTX	Benucci *et al.* 2009[153]	?	2 years	2 cDMARDs	$25k
	ADA + MTX	Wailoo *et al.* 2008[176]	?	Lifetime	No bDMARDs	$92k
	IFX + MTX	Wailoo *et al.* 2008[176]	?	Lifetime	No bDMARDs	Dominates
	IFX + MTX	Barton *et al.* 2004[152]	2000	Lifetime	SSZ and MTX	£28k
	IFX + MTX	Jobanputra *et al.* 2002[162]	2000	Lifetime	SSZ and MTX	£35k
	IFX + MTX	Nuijten *et al.* 2001[169]	1999	1 year	2 cDMARDs	Dominates
	ETN	Choi *et al.* 2002[157]	1999	6 months	MTX	$43k (per ACR 20 response), $35k (per ACR 70 response)
IFX + MTX	MTX	Bansback *et al.* 2005[150]	2001	Lifetime	2 previous cDMARDs	Euro 48k

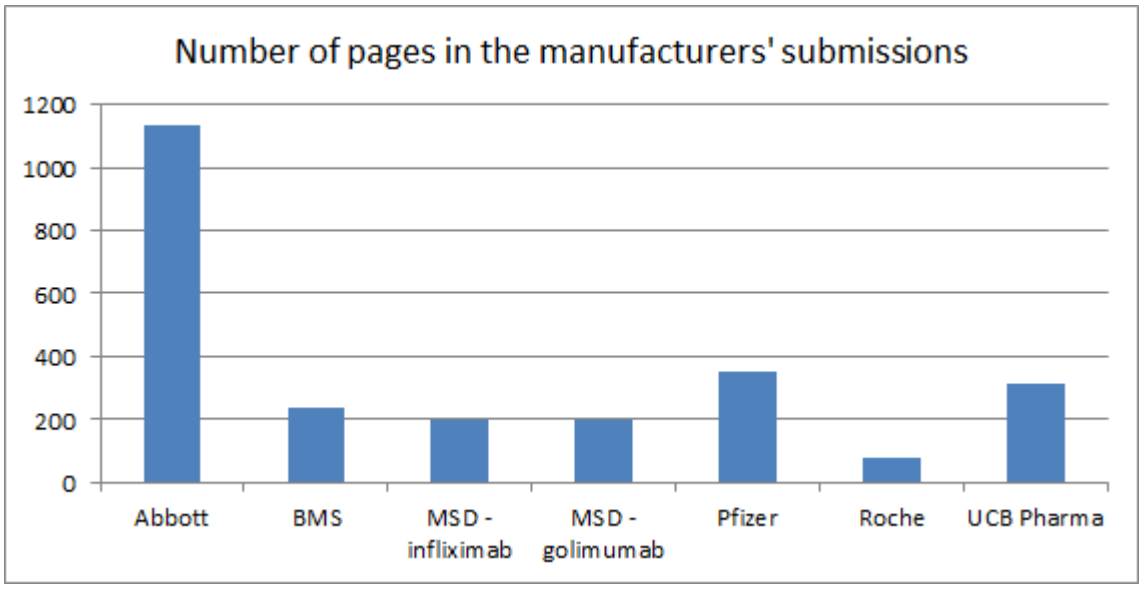
Drug	Comparator	Study	Price Year	Time horizon	Previous treatments	ICER (per QALY gained)
	MTX	Barbieri *et al.* 2005[151]	2000	1 year/Lifetime	cDMARDs and resistent to MTX	£34k (1 year), £24k (Lifetime)
	MTX	Kobelt *et al.* 2003[163]	?	10 year	cDMARDS including MTX IR	£22k
	MTX	Marra *et al.* 2007[168]	2002	10 year	cDMARDs	$46k
	MTX	Wong *et al.* 2002[178]	1998	Lifetime	MTX	$307k
	LEF	Rubio-Terrés *et al.* 2001[170]	1999	1 year	cDMARDs (inc MTX)	Dominated (CMA)
	cDMARDs	Barton *et al.* 2004[152]	2000	Lifetime	SSZ and MTX	£68k
	cDMARDs	Jobanputra *et al.* 2002[162]	2000	Lifetime	SSZ and MTX	£89k
	cDMARDs	Lekander *et al.* 2010[167]	2007	20 year	no aTNFs	Euro 23k
	cDMARDs	Chen *et al.* 2006[113]	2004	Lifetime	2 previous cDMARDs	£30-140k
	Anakinra	Chiou *et al.* 2004[156]	2003	1 year	Unclear	Dominated
	ADA + MTX	Wailoo *et al.* 2008[176]	?	Lifetime	No bDMARDs	Dominated
	ETN + MTX	Wailoo *et al.* 2008[176]	?	Lifetime	No bDMARDs	Dominated
TCZ + MTX	ETA + MTX	Diamantopoulos *et al.* 2012[160]	2009	Lifetime	cDMARDs	Dominates
	ADA + MTX	Diamantopoulos *et al.* 2012[160]	2009	Lifetime	cDMARDs	Dominates
	IFX + MTX	Diamantopoulos *et al.* 2012[160]	2009	Lifetime	cDMARDs	Euro 3k
	Add TCZ into first biologic	Diamantopoulos *et al.* 2012[160]	2009	Lifetime	cDMARDs	Euro 17k

Drug	Comparator	Study	Price Year	Time horizon	Previous treatments	ICER (per QALY gained)
	position					
	MTX	Soini *et al.* 2012[171]	2010	Lifetime	At least 1 cDMARD	Euro 19k
Grouped bDMARDs	cDMARD	Brennan *et al.* 2007[155]	2004	Lifetime	At least 2cDMARDs	£24k
	Previous years' DMARD use	Kobelt *et al.* 2004[164]	2002	1 year	2 cDMARDS including MTX IR	Euro 44k
TNFa	LEF	Welsing *et al.* 2004[177]	?	5 year	cDMARDs	Euro 544k

6.2 Critique of the manufacturers' submissions

The Assessment Group received submissions for seven interventions.[145,146,179-183] These were from six manufacturers as golimumab and infliximab are both manufactured by MSD. The submission by BMS evaluated both the intravenous and subcutaneous formulation of abatacept. The length and quality of the submissions varied. For information Figure 13 details the number of pages within each manufacturer's submission. In addition each submission contained a mathematical model.

Figure 13: The number of pages in each submission (including appendices)



An initial review of the submissions indicated that there were a multitude of methods employed and that attempting to summarise all seven submissions individually would likely not aid the reader. With this aim, the submissions have been summarised jointly under a number of categories to allow the reader to compare and contrast the methodologies used. This would remove the need for cross-referencing were the reader wanting to know the different assumptions made for a key variable or to quickly compare outputs from the model. Formal evaluation of these models using checklists such as the BMJ or Eddy checklists[184,185] was not possible within the timescales of the assessment however clear deviances from recommended methods have been outlined in the critique.

Where appropriate tables and figures will be taken from the manufacturers' submissions. Minor amendments, such as to the intervention abbreviations have been made to ensure consistency throughout the report.

The broad headings chosen were the:

- Decision Problem Addressed

- Strategies modelled
- Model Structure / Time Cycle
- Time Horizon
- Perspective
- Discounting
- Population characteristics
- Costs of Intervention
- Costs of administration and monitoring
- Comparative treatment efficacy (Mixed Treatment Comparison)
- Responder criteria
- HAQ / EQ-5D changes in relation to response levels
- HAQ trajectory following initial response
- Time to discontinuation of treatment
- Rebound post-treatment
- Assumed NHS costs per HAQ band
- Utility related to HAQ
- Assumed costs and disutilities associated with adverse events
- Mortality associated with RA
- Cost-effectiveness results
- Cost implications within England and Wales

6.2.1 Decision Problem Addressed

Tables 74 summarises the decision problems addressed within the manufacturers' submissions for those drugs that are licensed as monotherapy and for those that cannot. No detailed information is given in the tables which serve as reference only, with subtleties regarding each analysis provided in later sections. Four interventions (abatacept iv, abatacept sc, certolizumab and tocilizumab) are not licenced before the use of MTX. Four interventions (abatacept iv, abatacept sc, golimumab and infliximab) are not licenced as monotherapy.

6.2.1.1 Summary

It is seen that there was considerable variation in the decision problems addressed by the manufacturers with only the submissions by AbbVie and UCB evaluating all the subgroups both within the scope and the licence of their product.

Table 74: The decision problem addressed within the manufacturers' submission

			Manufacturer						
Analysis	Decision Problem	Scope	AbbVie (ADA)	BMS (ABT)	MSD (GOL)	MSD (IFX)	Pfizer (ETN)	Roche (TCZ)	UCB (CTZ)
1	Population 2 in combination with MTX	✔	✔		✔	✔	✔		✔
2	Population 3 in combination with MTX	✔	✔				✔		✔
3	Population 1 in combination with MTX	✔	✔				✔		
4	Population 2 monotherapy	✔	✔				✔		✔
5	Population 3 monotherapy	✔	✔						✔
6	Population 1 monotherapy	✔	✔						
7	General RA Population who can tolerate MTX [Δ]			✔	✔	✔			
8	MTX intolerant or contraindicated RA population †							✔	

Shaded cells indicate the intervention is not licensed in this population
ADA = adalimumab; ABT = abatacept; GOL = golimumab; IFX = infliximab; ETN = etanercept; TCZ = Tocilizumab; CTZ = certolizumab pegol; MTX = MTX. iv = intravenous; sc = subcutaneous

[Δ] In essence, analyses 1 and 2 combined † In essence, analyses 4 and 5 combined.

6.2.2 Strategies Modelled

The strategies modelled for each submission have been detailed individually for each manufacturer collated by the analyses numbers provided in the Decision Problem addressed section. These are:

1. Population 3 in combination with MTX
2. Population 2 in combination with MTX
3. Population 1 in combination with MTX
4. Population 3 monotherapy
5. Population 2 monotherapy
6. Population 1 monotherapy
7. General RA Population who can receive MTX
8. MTX intolerant or contraindicated RA population

6.2.2.1 In summary, most strategies appeared reasonable although it is noted that there were a few anomalies compared with NICE guidance or intervention licences:

- MSD (golimumab and infliximab) and UCB (certolizumab pegol) assumed that tocilizumab would not be used following rituximab;
- MSD assumed in one strategy that rituximab could be used without a bDMARD having been provided previously
- Pfizer (etanercept) assumed that abatacept iv would be used third-line if tocilizumab was used first line.
- Roche (tocilizumab) assumed a standard sequence of care for those intolerant of contra-indicated to MTX that included three lines of bDMARDs, and evaluated only one sequence where tocilizumab was inserted as the first-line treatment to create four lines of bDMARDs.
- Importantly UCB did not compare with a cDMARD-only option for Analyses 1 and 4.

6.2.2.2 AbbVie

The strategies employed in the AbbVie submission are contained in Tables 75 to 78. These appear appropriate.

Table 75: Strategies modelled by AbbVie for Analyses 1 and 2

Sequences								
Line 1	LEF	ADA+MTX	ETN+MTX	IFX+MTX	CTZ+MTX	GOL+MTX	ABT+MTX	TCZ+MTX
Line 2	SSZ	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
Line 3	CYC	TCZ+MTX	TCZ+MTX	TCZ+MTX	TCZ+MTX	TCZ+MTX	TCZ+MTX	LEF
Line 4	Rescue	LEF	LEF	LEF	LEF	LEF	LEF	SSZ
Line 5		SSZ	SSZ	SSZ	SSZ	SSZ	SSZ	CYC
Line 6		CYC	CYC	CYC	CYC	CYC	CYC	Rescue
Line 7		Rescue	Rescue	Rescue	Rescue	Rescue	Rescue	

ABT – abatacept iv; ADA – adalimumab; CTZ – certolizumab; CYC – cyclosporine; ETN – etanercept; GOL – golimumab; IFX - infliximab; LEF – leflunomide; MTX – MTX, RTX – rituximab; SSZ – sulfasalazine, TCZ – tocilizumab.

Table 76: Strategies modelled by AbbVie for Analysis 3

Sequences						
Line 1	MTX	ADA+MTX	ETN+MTX	IFX+MTX	GOL+MTX	MTX+HCQ
Line 2	SSZ	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	ADA+MTX
Line 3	HCQ	TCZ+MTX	TCZ+MTX	TCZ+MTX	TCZ+MTX	RTX+MTX
Line 4	LEF	LEF	LEF	LEF	LEF	TCZ+MTX
Line 5	CYC	SSZ	SSZ	SSZ	SSZ	LEF
Line 6	Rescue	CYC	CYC	CYC	CYC	SSZ
Line 7		Rescue	Rescue	Rescue	Rescue	CYC
Line 8						Rescue

ADA – adalimumab; CYC – cyclosporine; ETA – etanercept; GOL – golimumab; HCQ – hydrixychlorine; INF - infliximab; LEF – leflunomide; MTX – MTX, RTX – rituximab; SSZ – sulfasalazine, TOC – tocilizumab.

Table 77: Strategies modelled by AbbVie for Analyses 4 and 5

Sequences					
Line 1	SSZ+HCQ	ADA	ETN	CTZ	TCX
Line 2	LEF	LEF	LEF	LEF	LEF
Line 3	SSZ	SSZ	SSZ	SSZ	SSZ
Line 4	CYC	CYC	CYC	CYC	CYC
Line 5	Rescue	Rescue	Rescue	Rescue	Rescue

ADA – adalimumab; CTZ – certolizumab; CYC – cyclosporine; ETN – etanercept; HCQ – hydrixychlorine; LEF – leflunomide; SSZ – sulfasalazine; TCZ – tocilizumab.

Table 78: Strategies modelled by AbbVie for Analysis 6

Sequence	1	2	3	4
Line 1	SSZ+HCQ	ADA	ETN	SSZ+HCQ
Line 2	LEF	LEF	LEF	ADA
Line 3	SSZ	SSZ	SSZ	LEF
Line 4	CYC	CYC	CYC	SSZ
Line 5	Rescue	Rescue	Rescue	CYC
Line 6				Rescue

ADA – adalimumab; CYC – cyclosporine; ETA – etanercept; HCQ – hydrixychlorine; LEF – leflunomide; SSZ – sulfasalazine.

6.2.2.3 BMS

The strategies employed in the BMS submission are contained in Table 79. These appear appropriate. The analyses assumed that if a patient had an adverse event within the first 6 months that a randomly sampled (and previously unused bDMARD would be used instead).

If a patient was contraindicated to rituximab then a randomly sampled (and previously unused bDMARD would be used instead).

From the model structure it appears that if there is a good response to rituximab then tocilizumab would not be used as a third line treatment option.

Table 79: Strategies modelled by BMS for Analyses 1 and 7

Sequences									
1	LEF	ABT sc +MTX	ABT sc +MTX	ADA +MTX	CTZ +MTX	ETN +MTX	GOL+MTX	IFX+MTX	TCZ+MTX
2	GLD	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
3	CYC	TCZ+MTX*	TCZ+MTX*	TCZ+MTX	TCZ+MTX*	TCZ+MTX*	TCZ+MTX*	TCZ+MTX	LEF
4	AZA	LEF	LEF	LEF	LEF	LEF	LEF	GLD	GLD
5	PC	GLD	GLD	GLD	GLD	GLD	GLD	CYC	CYC
6		CYC	CYC	CYC	CYC	CYC	CYC	AZA	AZA
7		AZA	AZA	AZA	AZA	AZA	AZA	PC	PC
8		PC	PC	PC	PC	PC	PC		

ABT iv – abatacept iv; ABT sc – abatacept sc; ADA – adalimumab; AZA – azathioprine; CTZ – certolizumab; CYC – cyclosporine A; ETN – etanercept; GOL – golimumab; GLD = injectable gold; INF - infliximab; LEF – leflunomide; MTX – MTX, PC – palliative care; RTX – rituximab; TCZ – tocilizumab

* It appears that TCZ + MTX would not be used if there was a DAS28 improvement of 1.2 or greater at six months

6.2.2.4 MSD

For brevity the strategies for golimumab and infliximab have been discussed jointly as they are identical. The strategies employed in the MSD submissions are contained in Table 80. It is noted that these do not allow tocilizumab to be used as a third line biologic as allowed within NICE guidance. MSD assume that the first and second line treatment options have been used prior to the decision point. The Assessment Group comment that the use of rituximab in the MTX arm is outside of licence as a bDMARD must have been provided prior to rituximab.

Table 80: Strategies modelled by MSD for Analyses 1 and 7

Treatment stage	Infliximab arm	Golimumab arm	Other biologic DMARD arm	MTX arm
1st line treatment	*MTX*	*MTX*	*MTX*	*MTX*
2nd line treatment	*Sulfasalazine + MTX*	*Sulfasalazine + MTX*	*Sulfasalazine + MTX*	*Sulfasalazine + MTX*
3rd line treatment	Infliximab + MTX	Infliximab + MTX	Biologic DMARD + MTX	MTX
4th line treatment	Rituximab	Rituximab	Rituximab	Rituximab
5th line treatment	Leflunomide	Leflunomide	Leflunomide	Leflunomide
6th line treatment	Gold	Gold	Gold	Gold
7th line treatment	Azathioprine	Azathioprine	Azathioprine	Azathioprine
8th line treatment	Ciclosporin	Ciclosporin	Ciclosporin	Ciclosporin
9th line treatment	Palliative care	Palliative care	Palliative care	Palliative care

The other bDMARDs evaluated were: etanercept; adalimumab; certolizumab; tocilizumab; abatacept iv and abatacept sc.

6.2.2.5 Pfizer

The strategies employed in the Pfizer submission are contained in Table 81. It is noted that the strategy with tocilizumab first does not follow NICE guidance in that abatacept iv is used as a third-line treatment.

Table 81: Strategies modelled by MSD for Analyses 1,2 and 3

Tx line†	ETN	ABTiv	ABTsc	CTZ	ADA	IFX	TCZ	GOL	cDMARD	Comb cDMARD
1	ETN	ABTiv	ABTsc	CTZ	ADA	INF	TCZ	GOL	cDMARD	Comb cDMARD
2	RTX	RTX	RTX	RTX	RTX	RTX	RTX	RTX	RTX	RTX
3	TCZ	TCZ	TCZ	TCZ	TCZ	TCZ	ABTiv	TCZ	TCZ	TCZ
4	SSZ	SSZ	SSZ	SSZ	SSZ	SSZ	SSZ	SSZ	SSZ	SSZ
5	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF
6	PC	PC	PC	PC	PC	PC	PC	PC	PC	PC
Treatment sequences applied by population ✔ = primary analysis, ✔ = secondary analysis (note analysis with alternative second line not shown)										
DMARD-IR combination	✔	✔	✔	✔	✔	✔	✔	✔	✔	
Moderate to Severe	✔			✔					✔	
Severe Naïve	✔				✔				✔	✔

ABT iv – abatacept iv; ABT sc – abatacept sc; ADA – adalimumab; AZA – azathioprine; cDMARD – conventional DMARD; comb cDMARD – combination cDMARDs; CTZ – certolizumab; CYC – cyclosporine A; ETN – etanercept; GOL – golimumab; INF - infliximab; LEF – leflunomide; PC – palliative care; RTX – rituximab; TCZ – tocilizumab.

Table 82: Strategies modelled by MSD for Analysis 4

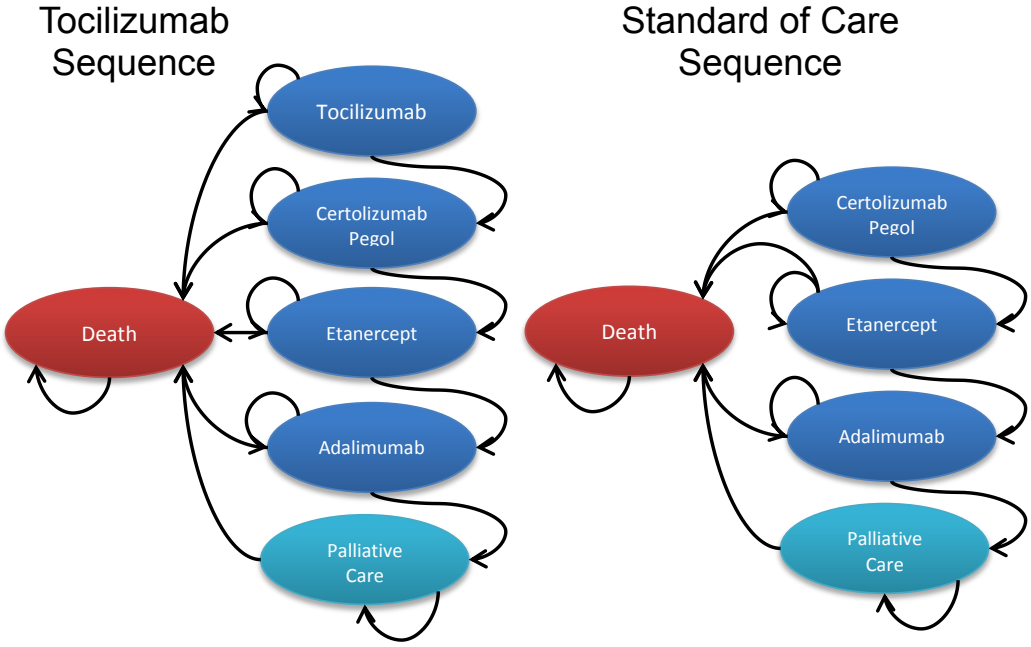
Tx line	ETN	ADA	TOC1	TOC2	cDMARD
1	ETN	ADA	TOC	TOC	cDMARD
2	ADA	ETN	ETN	ADA	ETN
3	SUL	SUL	SUL	SUL	SUL
4	LEF	LEF	LEF	LEF	LEF
5	PC	PC	PC	PC	PC

ADA – adalimumab; AZA – azathioprine; ETN – etanercept; LEF – leflunomide; PC – palliative care; TCZ – tocilizumab.

6.2.2.6 Roche

Roche evaluated a very limited set of sequences which consisted of inserting tocilizumab before a standard sequence of care. This is replicated in Figure 14. Roche only evaluated a sequence of MTX intolerant or contraindicated RA population. It is noted that Roche assumes that the standard of care sequence has three lines of bDMARD treatments (followed by palliative care) which is not in accordance with current NICE guidance. Roche evaluated only one sequence where tocilizumab was inserted as the first-line treatment to create four lines of bDMARDs.

Figure 14: Strategies modelled by Roche for analysis 8



6.2.2.7 UCB

The strategies modelled by UCB are given in Table 83. The assessment note that in the MTX experienced populations with DAS>5.1 that continuing use of cDMARDs was not a comparator strategy which is a serious deviation from the published scope.

Table 83: Strategies modelled by UCB for Analyses 1 and 4

Set-up	Interventions/regimens	Justification
Comparators	**Combination with MTX** Certolizumab pegol Adalimumab Etanercept Golimumab Tocilizumab Infliximab Abatacept **Monotherapies** Certolizumab pegol Adalimumab Etanercept Tocilizumab	Treatment comparators are based on scope set by NICE and the availability of efficacy data for included studies in the mixed treatment comparison and network analysis of trials. For golimumab, infliximab and abatacept, only combinations with MTX were analysed based on the licences of the biologics and the NICE scope.
Follow-on interventions	Rituximab + MTX Azathioprine Cyclosporine Gold Hydroxychloroquine Leflunomide Penicillamine Palliation	Follow-on treatments are common to all comparators in the model; rituximab + MTX is the first treatment comparator on the basis of NICE appraisal TA195. Follow-up with cDMARDs is based on the sequence of follow-on treatments considered in previous technology appraisals.[119]

Table 84: Strategies modelled by UCB for Analyses 2 and 5

Set-up	Parameter	Justification
Comparators	Certolizumab pegol + MTX Certolizumab pegol + cDMARDs Placebo + MTX Placebo + cDMARDs	Treatment comparators are based on scope set by NICE and the availability of efficacy data for included studies in the mixed treatment comparison and network analysis of trials
Follow-on interventions	MTX + sulfasalazine MTX + sulfasalazine + hydroxychloroquine MTX + hydroxychloroquine MTX + leflunomide Sulfasalazine + hydroxychloroquine Cyclosporine Penicillamine Palliation	Follow-up with cDMARDs is based on the sequence of follow-on treatments considered in previous technology appraisals.

6.2.3 Model Structure / Time cycle

This section details the model structure employed by each manufacturer. The two submissions from MSD have been assessed jointly due to having the same structure.

6.2.3.1 Broad Summary

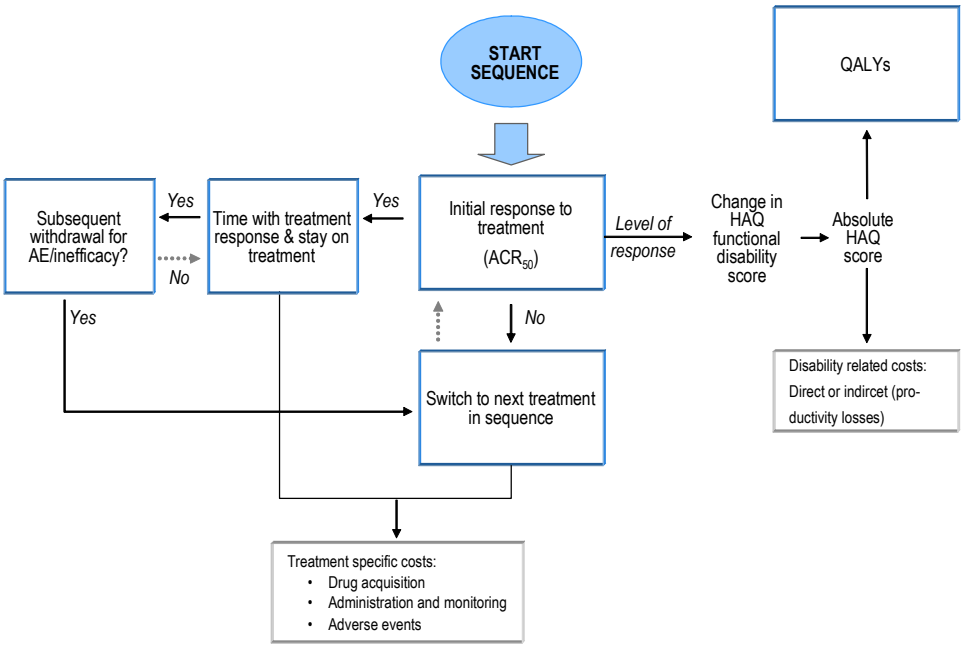
Four individual patient models and two cohort models were submitted. Of the four individual patient level models three used discrete event simulation (DES) techniques, which do not need time cycles, with the remainder using a 6 month cycle. Of the two cohort models one used a six month time cycle, whilst the other adopted this after the initial year, with either three cycles of 6, 3 and 3 months in the first year, or 3, 4.5 and 4.5 months depending on the user input. Both cohort models used a half-cycle correction.

Four of the models were constructed in Microsoft Excel (©Microsoft Corporation); one in Arena (©Rockwell Automation); and one in Simul8 (©Simul8 Corporation)

6.2.3.2 AbbVie

The model is an individual patient simulation based within Arena (©Rockwell Automation) run for a cohort of 1,000 patients, each with specific baseline characteristics, which are sampled from distributions specified in an Excel input shell. 150 replications are done for each analysis to create 150,000 patients per treatment sequence. The overview of the model logic is shown in Figure 15. The model uses a discrete event simulation approach thus there are no time cycles, although all patients are assumed to stay on treatment for 6 months (unless an AE occurs)

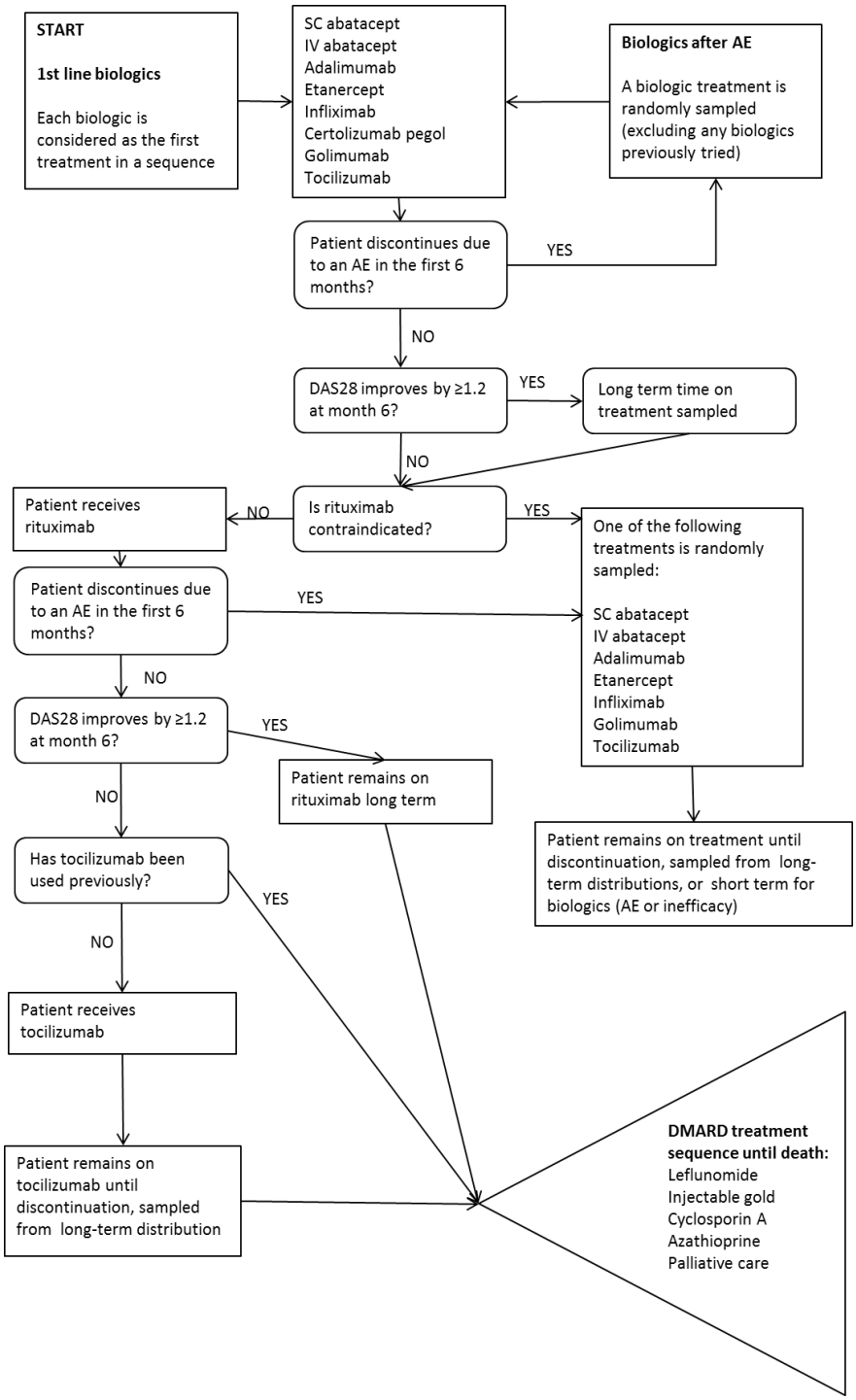
Figure 15: The AbbVie Model Structure



6.2.3.3BMS

BMS reproduced the individual patient model built by Malottki et al.[186] but added first-line biologics to the beginning of the model. This was implemented in Simul8 (©Simul8 Corporation) and does not require time cycles. The model logic is shown in Figure 16.

Figure 16: The BMS Model Structure



6.2.3.4 MSD

A Markov model constructed in Excel (© Microsoft Corporation) was used to estimate the expected costs and QALYs of patients with RA. A time cycle of six months was used with half-cycle correction.

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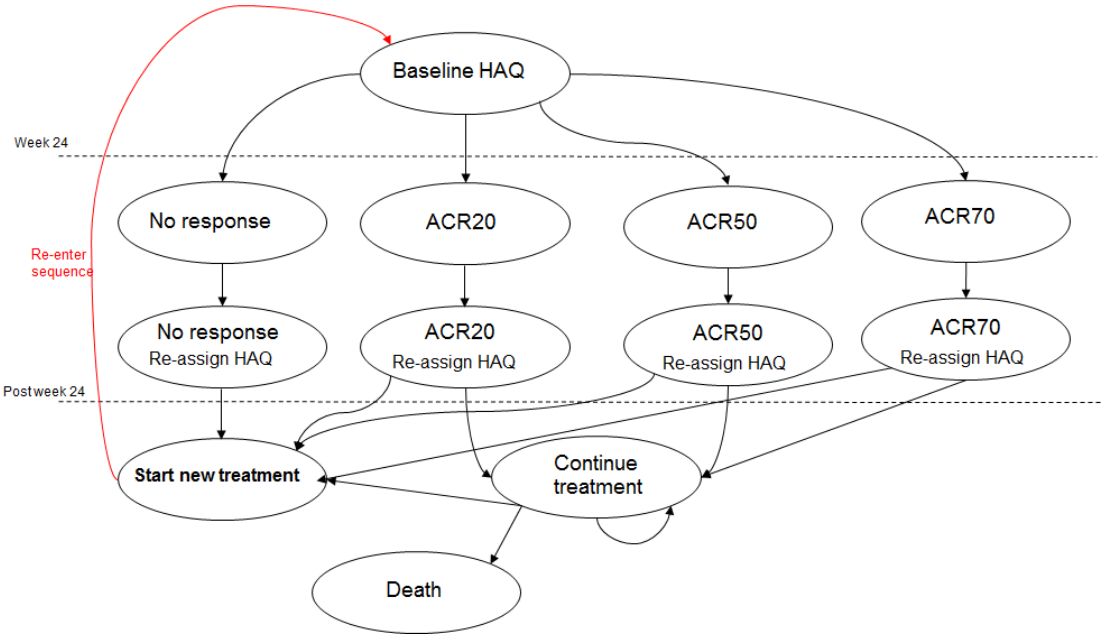
Figure 17: The MSD Model Structure



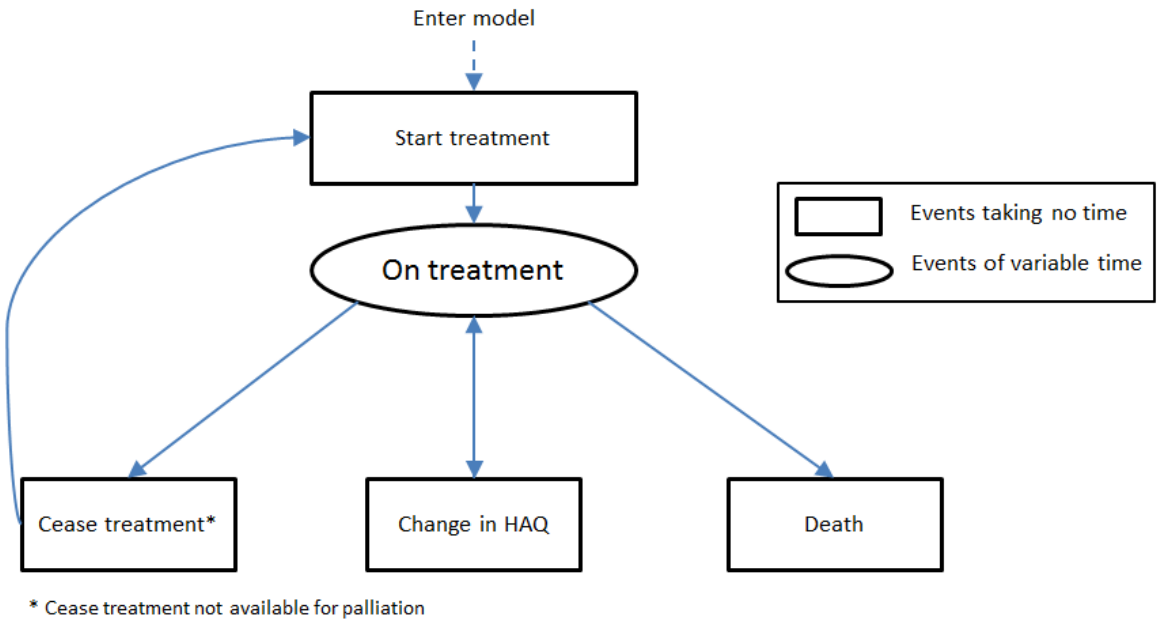
6.2.3.5 Pfizer

The model was developed in Microsoft Excel (©Microsoft Corporation) with Visual Basic for Applications and uses a DES approach to model individual patients. As the model uses a DES approach no time cycles were necessary.

Time on treatment and disease progression are time-dependent, whilst modelling the effects of treatment withdrawal, and any subsequent rebound effect, requires knowledge of patients' disease status prior to treatment.

The model structure is summarised in Figure 18 and is applicable to each decision problem evaluated.

Figure 18: The Pfizer Model Structure



Abbreviations: HAQ, Health Assessment Questionnaire

6.2.3.6 Roche

The manufacturer reports that the design of the economic analysis follows guidelines set by the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) Economics Working Group.[187,188]

The economic analysis is based on an individual patient model designed in Microsoft Excel (©Microsoft Corporation) with the use of visual basic applications. The model tracks the characteristics of the individuals and maintains a history in particular of a patient's response to treatment in their assigned drug sequence and change in HAQ score over time.

The model algorithm is presented in Figure 19:

Figure 19: The individual simulation process reported by Roche

Start the simulation

For patients $i=1, 2, \ldots, n$, cycles $k=1, 2, \ldots, n$ a random number drawn by a continuous uniform distribution $\theta \sim U[0,1]$, and the relevant risk factor p.

Determine the path of patient i through the model by $\theta_{i,k} \leq p_k$

Determine cost c_i and utility u_i for individual i

End the simulation

Estimate the mean cost and utility $E[(C, U)]$ by

$$\hat{a}_n = \frac{1}{n}\sum_{i=1}^{n}(c_i, u_i)$$

The model implements a 6 month cycle length, which is in line with timing of available efficacy evidence (ACR data). Patients transition through the model by sequentially moving on to each treatment. Once patients exhaust all treatments in the sequence, they move into palliative care where they remain until death.

6.2.3.7 UCB

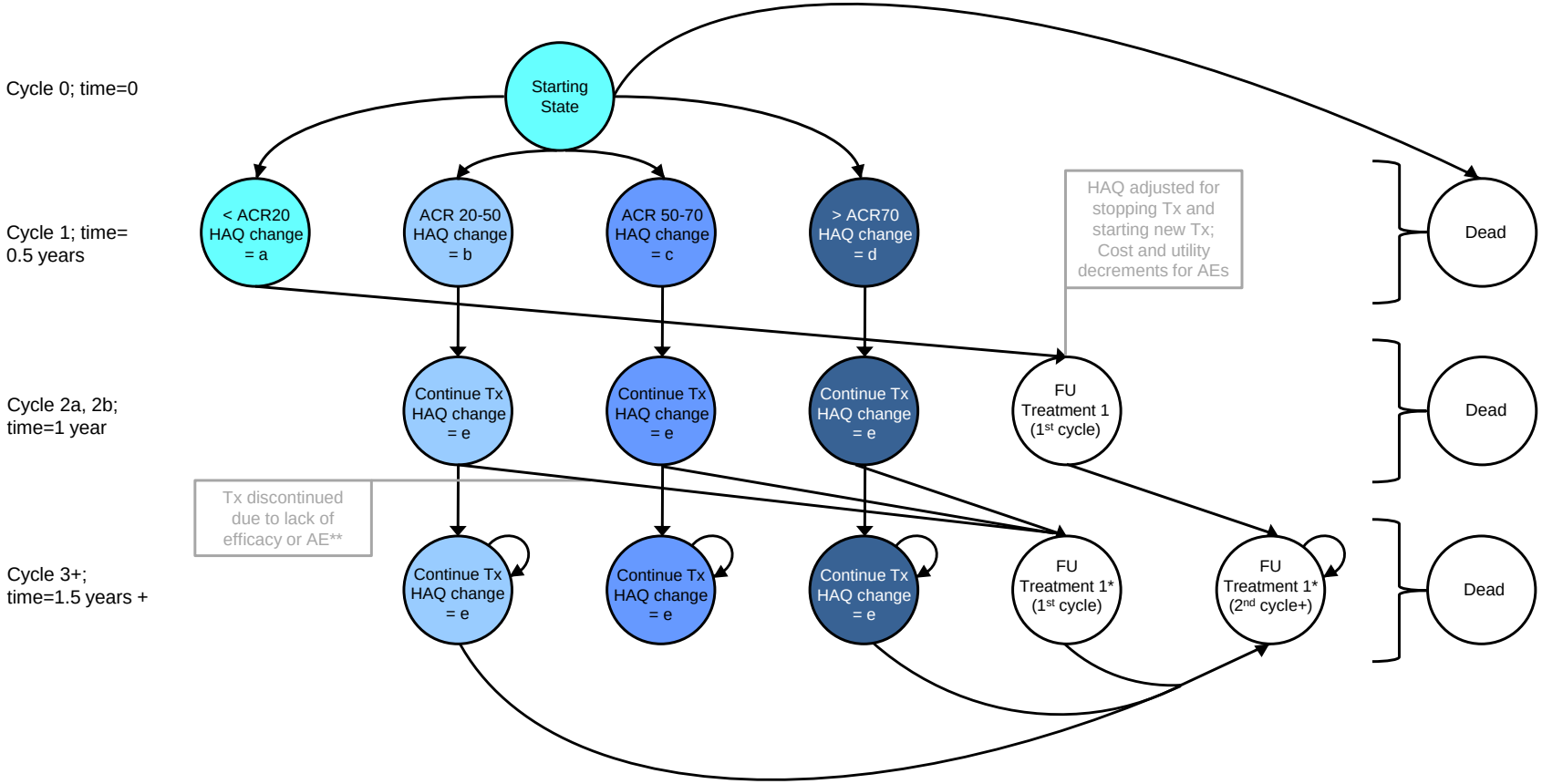
The cost-effectiveness model is a Markov (cohort health state transition) structure constructed in Microsoft Excel.

The first model cycle is either 3 or 6 months (12 or 24 weeks), depending on the definition of response selected in the model and reflective of the published clinical guidance (6 months (24 weeks) is used in the base case). The model allows for clinical response to be measured by either ACR response criteria (developed by the American College of Rheumatology), or EULAR response criteria (developed by the European League Against Rheumatism).

There are two further model cycles in the first year which are common to both the severe and moderate disease activity populations. Where the first model cycle has been chosen to be 3 months, the subsequent two time-steps are each 4.5 months long. Where the first model cycle has been chosen to be 6 months, the subsequent two time-steps are each 3 months long. The maximum time-step length in the model is 6 months.

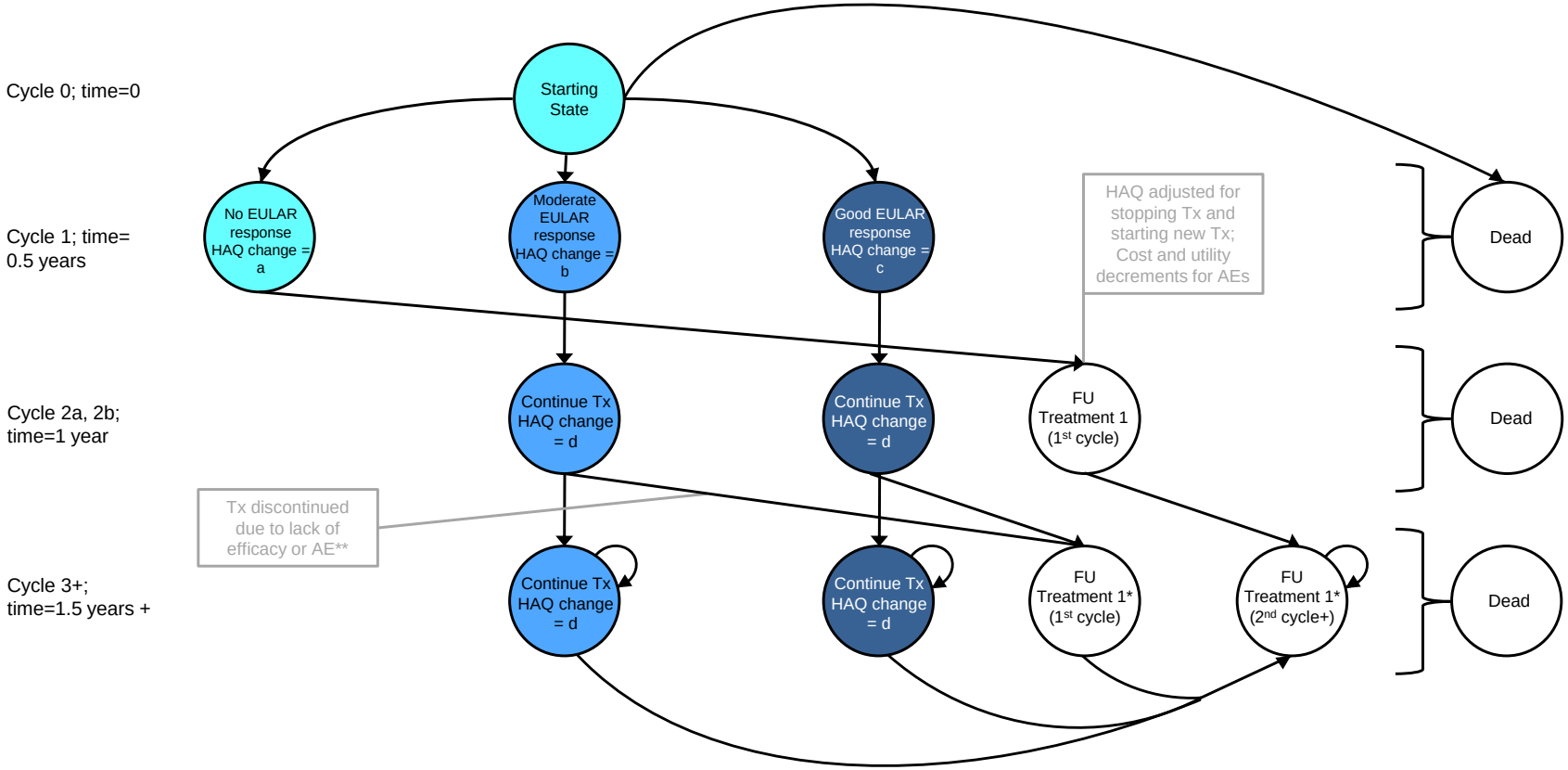
At the end of the next and following cycles, patients may remain in the same Markov state, discontinue treatment due to an adverse event, discontinue treatment due to lack of efficacy or intolerance, or die. There are no state transitions other than discontinuation of treatment and death. Discontinuation of treatment was assumed to be the same for all comparators, which was deemed to be a conservative assumption. Transition probabilities were calculated to appropriately reflect the varying length of time-steps in the first model year. After the first 12 months, the cycle length is 6 months, reflecting the frequency of monitoring recommended by NICE and the British Society of Rheumatology. A half-cycle correction was employed.

Figure 20: Markov structure – severe disease activity population; model structure based on ACR response



*Follow-up treatment states: duplicated for each follow-up treatment. Patients not responding in first 6 months of follow-up treatment will move to the next treatment in the sequence; **Reason for discontinuation (lack of efficacy) governed by probabilities after leaving treatment health state.
HAQ-DI categories relate to the non-treatment specific costs associated with disability.

Figure 21: Markov structure – moderate disease activity population; model structure based on EULAR response



*Follow-up treatment states: duplicated for each follow-up treatment. Patients not responding in first 6 months of follow-up treatment will move to the next treatment in the sequence; **Reason for discontinuation (lack of efficacy) governed by probabilities after leaving treatment health state.
HAQ-DI categories relate to the non-treatment specific costs associated with disability.

6.2.4 Time Horizon

The time horizon for each model is detailed below. In summary, all models adopted a lifetime, or approximately lifetime time horizon.

6.2.4.1 AbbVie

The AbbVie model used a lifetime horizon

6.2.4.2 BMS

The BMS model used a lifetime horizon

6.2.4.3 MSD

The MSD model used a time horizon of 45 years, assuming that patients with moderate to severe RA would die at a maximum 95 years and those with severe RA would die at a maximum age 96 years. Shorter analysis timeframes were used in the sensitivity analyses.

6.2.4.4 Pfizer

The Pfizer model used a lifetime horizon. Shorter analysis timeframes were used in the sensitivity analyses.

6.2.4.5 Roche

The BMS model used a lifetime horizon

6.2.4.6 UCB

The time horizon in the base case analysis was an approximation of the lifetime of a patient. UCB stated that analysis of BSRBR data has revealed an average age of patients starting on TNF inhibitors of 55 years.[189] A timeframe of 45 years would assume that patients would die at a maximum age of 100 years. Shorter analysis timeframes were used in the sensitivity analyses.

6.2.5 Perspective

The perspectives adopted in the submissions are detailed below. In summary, all submissions used an NHS and personal social services perspective

6.2.5.1 AbbVie

The base case analysis of the economic evaluation was conducted from an NHS and Personal Social Services perspective. AbbVie note that resource use data related to Personal and Social Services for the management of RA in the UK were not available for costing purposes.

6.2.5.2 BMS

Whilst not explicitly stated the BMS model adopts a NHS and personal social services perspective

6.2.5.3 MSD

The MSD analysis is conducted from the UK NHS perspective. Direct costs included the drug cost, administration cost, and heath care resource use.

6.2.5.4 Pfizer

The current analysis was conducted from the perspective of the UK National Health Service (NHS) and Personal Social Services.

6.2.5.5 Roche

The Roche submission used an NHS and personal social services perspective.

6.2.5.6 UCB

The model takes a payer perspective (i.e. that of the NHS and Personal Social Services (PSS)), as per NICE guidance, and includes direct medical costs such as hospital care (inpatient and outpatient), primary care and home visits. Sensitivity analyses were conducted using a societal perspective.

6.2.6 Discounting

The discount rates used within the submissions are shown in Table 85. In summary, each submissions used the appropriate discount rate in the base case analysis.

Table 85: The discount rates used per annum within the submissions

Manufacturer	**Base Case**		**Sensitivity Analyses**	
	Costs	QALYs	Costs	QALYs
AbbVie	3.5%	3.5%	6.0%	1.5%
			1.5%	1.5%
BMS	3.5%	3.5%		
MSD	3.5%	3.5%	0.0%	3.5%
			3.5%	0.0%
			0.0%	0.0%
Pfizer	3.5%	3.5%	6.0%	1.5%
Roche	3.5%	3.5%		
UCB	3.5%	3.5%	6.0%	1.5%
			1.5%	6.0%
			1.5%	1.5%
			6.0%	6.0%

6.2.7 Population Characteristics

The population characteristics for each submission is detailed in this section. In summary the manufacturers often use drug specific data from the BSRBR, or from the trials related to their intervention. Typically no comment is made regarding the correlation between parameters with the exception of Pfizer's model.

6.2.7.1 AbbVie

The baseline characteristics for patients considered within the AbbVie analyses come from different sources, of which it was stated that wherever possible the source were chosen to reflect the composition of the treated population for RA in the UK. For MTX-experienced patients with moderate disease activity the source was the ReAct study.[190] Data from the British Society of Rheumatology Biologics Register (BSRBR) for this patient population could not be used, because historically patients in the UK have always required a DAS28>5.1 to receive an anti-TNF; as such, any patients in the BSRBR with a DAS28<5.1 who received an anti-TNF are very select group of patients with non-normal characteristics. For MTX-experienced patients with severe disease activity the source was the BSRBR data AbbVie report that analysis was undertaken on BSRBR data for

adalimumab from raw BSRBR and this was presented as academic-in-confidence data. For MTX-naïve patients with severe disease activity the source was the PREMIER trial.[99] The characteristics of patients for each of those populations are outlined in Tables 86 to 88 No comment is made on the correlation of parameters.

Table 86: The baseline Patient Characteristics for MTX-experienced patients with moderate disease activity assumed by AbbVie

	Value	Source
Gender (% female)	81.4%	Burmester et al, 2007[190]
Age (years)	54.6	Burmester et al, 2007[190]
Baseline HAQ-DI	1.5 (0.65) †	Burmester et al, 2007[190]
Disease Duration (years)	10.65m (8.56) †	Burmester et al, 2007[190]

†mean (standard deviation)

Table 87: The baseline patient characteristics for MTX-experienced patients with severe disease activity assumed by AbbVie

	Value	Source
Gender (% female)	[redacted]	BSRBR
Age (years) *	[redacted]	BSRBR
Baseline HAQ-DI *	[redacted]	BSRBR
Disease Duration (years)	[redacted]	BSRBR

†mean (standard deviation); * males / females

Table 88: The baseline patient characteristics for MTX-naive patients with severe disease activity assumed by AbbVie

	Value	Source
Gender (% female)	75.0%	Breedveld et al., 2006[99]
Age (years) *	60.8 / 58.0	Breedveld et al., 2006[99]
Baseline HAQ-DI *	1.38 (0.62) † / 1.58 (0.65) †	Breedveld et al., 2006[99]
Disease Duration (years)	11.28 (9.07)	Breedveld et al., 2006[99]

†mean (standard deviation); * males / females

For each sub-population several sensitivity analyses were conducted, to take into account the effect in the cost-effectiveness estimates of applying the sequences to: a fully male or fully female population; a population with average starting age 55, or 65; a population with average baseline HAQ of 1.0, 1.5, or 2.0. There is no comment on the correlation assumed between the distributions.

6.2.7.2 BMS

The BMS patient-level simulation model generates a group of virtual patients, who are assigned individual characteristics, such that each patient has their own gender, age and HAQ score. These values were taken from Chen et al, and reproduced in Tables 89 and 90. It is not commented whether the age and gender distributions are assumed to be correlated with HAQ distribution.

Table 89: Age and Gender distributions of patients in the BMS model

	Age							
Gender	**15-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**Total**
Male	0.9%	2.5%	5.4%	8.3%	9.0%	6.8%	5.1%	38%
Female	1.5%	4.0%	8.8%	13.7%	14.7%	10.9%	8.4%	62%

Table 90: HAQ score distribution of patients in the BMS model

Starting HAQ-DI score	0.125	0.25	0.375	0.5	0.625	0.75	0.875	1	1.125	1.25	1.375	1.5
Patients	3.1%	6.7%	6.7%	5.8%	5.3%	4.9%	4.8%	3.1%	6.7%	6.7%	5.8%	6.3%
Starting HAQ-DI score	1.625	1.75	1.875	2	2.125	2.25	2.375	2.5	2.625	2.75	2.875	3
Patients	6.6%	7.0%	6.9%	6.2%	4.7%	2.7%	0.9%	0.1%	0%	0%	0%	0%

It is commented that the mean of the assumed duration is a HAQ of 1.22

6.2.7.3 MSD – Golimumab

It is reported that the basecase analysis reflects the GO-FORWARD[191] population and the subgroup analysis reflects the severe patient group (DAS>5.1) from GO-FORWARD. No comment is made on the correlation between parameters.

6.2.7.4 MSD – Infliximab

It is reported that the basecase analysis reflects the ATTRACT[67] population and the subgroup analysis reflects the severe patient group (DAS28 >5.1) from ATTRACT. No comment is made on the correlation between parameters.

6.2.7.5 Pfizer

The characteristics of patients used in the Pfizer model are subdivided into three groups: severe DMARD-IR; moderate to severe-IR; and severe naïve patients. The following text is taken largely from the Pfizer submission

Severe DMARD-IR

Characteristics of individual patients in the Severe DMARD-IR population were sampled (with replacement) directly from the baseline etanercept BSRBR patient cohort (Table 91).This method has the advantage of maintaining correlation between variables without reliance on strong distributional assumptions, such as multivariate normality, or complex copula-based processes to specify arbitrary marginal distributions. Table 91 presents a summary of the population characteristics assumed within the model for all populations.

Moderate to Severe DMARD-IR

The etanercept BSRBR cohort with DAS ≤ 5.1 was not considered sufficiently generalisable to the Moderate to Severe population. Patient characteristics for the Moderate to Severe population were simulated using summary statistics from PRESERVE,[192] with the correlation structure taken from the BSRBR (n=3,780). The implicit assumption is that the correlation between variables in these two populations is the same. The population was generated with no restrictions on DAS, and then an acceptance-rejection algorithm was used to redraw characteristics for patients in whom the simulated DAS28 was outside the 3.2 - 5.1 range or who had a simulated age < 18. This avoided any artificial truncation caused by, for example, assuming all patients simulated with a DAS28 < 3.2 had a DAS28 = 3.2 and preserved the correlation between variables.

Severe DMARD-Naïve patients

Patients within the etanercept BSRBR cohort enter the registry within the context of current clinical practice. As current clinical guidance from NICE does not permit the use of bDMARDs before the failure of two conventional DMARDs, the etanercept BSRBR cohort does not contain a patient population generalisable to the Severe DMARD-naïve population. In order to generate this cohort, characteristics were sampled using summary statistics from COMET, assuming the correlation structure from the etanercept BSRBR cohort. The simulation of patients used an acceptance/rejection criteria as described for moderate to severe DMARD-IR in order to ensure all patients had a DAS28 > 5.1 and age ≥ 18.

Table 91: The baseline characteristics of patients sampled in the Pfizer models.

	Severe DMARD-IR (ETN BSRBR cohort N=3,780)			Severe Naïve (COMET)		Moderate to Severe (PRESERVE)	
Variable	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Mean**	**SD**
HAQ	2.09	0.55	0.00 – 3.00	1.70	0.70	1.10	0.6
DAS28	6.73	0.85	5.11 – 9.20	6.50	1.00	4.40	0.40
Weight (kg)	73	17	33 – 178	73†	17	72‡	16
Age (years)	56.1	12.0	18.0 – 84.3	51.4	0.4	48.4	11.9
Female (%)	77			73		83	
DD (years)	14	9	0 – 64	1	0	7	7

Abbreviations: DAS, disease activity score-28 joints; DD, disease duration; DMARD-IR, disease modifying antirheumatic drug inadequate response; HAQ, Health Assessment Questionnaire; SD, standard deviation; † From ETN BSRBR cohort with DAS > 5.1; ‡ From ETN BSRBR cohort with DAS ≤ 5.1.

6.2.7.6 Roche

Roche report that the modelled patient population is consistent with both the drug license and populations from TCZ and comparator Phase III trials. The population comprises moderate to severe RA patients who have had an inadequate response to one or more traditional disease-modifying anti-rheumatic drugs (tDMARDs), and who are intolerant or contraindicated to MTX.

All baseline characteristics in the model are taken from the Phase IV ADACTA study with the exception of the average patient weight. The average patient weight in the ADACTA study was 77kg, significantly higher than previous estimates for the UK population.

Therefore Roche used the 70kg weight previously accepted in NICE technology appraisals. (TA 130, 195, and 247). The Assessment Group comment that the assumed lower weight assumed by Roche is likely to underestimate the costs of tocilizumab as a person weighing 70kg requires a 400mg and 200mg vial, whereas a person weighing 77kg would require an additional 80mg vial.

A summary of the patient characteristic data assumed by Roche is provided in Table 92. No comment is made on the correlation of the parameters.

Table 92: The patient characteristic data assumed by Roche

Parameter	Value
Gender: Female	79%
Mean age	53.8
Mean weight (kg)*	70
Starting HAQ score	1.65

Source: ADACTA. * Based on previous HTA assessment estimates in RA.

6.2.7.7 UCB

UCB simulated patients with RA and a moderate or severe disease activity who have had an inadequate response to MTX. The cost-effectiveness of certolizumab pegol vs. alternative treatments was evaluated separately for the moderate and severe disease activity populations.

Baseline characteristics of the severe RA population and the moderate to severe RA population were based on mean estimates from the certolizumab pegol trials, which were assumed to reflect the population eligible for treatment with certolizumab pegol in clinical practice (Table 93). Baseline characteristics for the severe disease activity population were based on the pooled estimates from RAPID 1[129], RAPID 2[130] and FAST4WARD[193]studies (including both the certolizumab pegol and placebo treatment arms). Baseline characteristics for the moderate disease activity population were based on estimates from the CERTAIN[71] study (including both the CZP and PBO treatment arms). Some data were presented as academic-in-confidence. No comment is made on the correlation between parameters.

Table 93: The baseline characteristics of the modelled population assumed by UCB

Characteristic	Severe disease activity population	Moderate disease activity population
Age (years), mean	52.2	53.7
Gender (% female)	82.7%	80.4%
HAQ score, mean	1.62	[redacted]
Utility (EQ-5D score)*, mean	0.38	[redacted]
Number of previous DMARDs, mean	1.34	1.12
Disease duration (years), mean	6.54	4.61
Antibody status (% negative)	92.9%	100%

*Utility weight estimates were based on the pooled data from the RAPID 1 and RAPID 2 trials for the severe RA population, and on the CERTAIN study for the moderate RA population

6.2.8 The assumed costs of the interventions

This section details the costs assumed by each manufacturer; administration and monitoring costs are included in a separate section. In summary the costs seem appropriate apart from the following points: AbbVie do not consider current patient access schemes; BMS assume that all patients weigh 70kg which is likely to underestimate the costs for weight-based dosages (bar golimumab); none of MSD, Pfizer and UCB include patient access schemes for tocilizumab or abatacept as these are commercial-in-confidence, Roche assume a constant patient weight.

All manufacturers assumed vial wastage for abatacept iv, tocilizumab and infliximab, although Roche discuss that where the appropriate dose is only marginally above that produced by a combination of vials a clinician may not opt to open a new vial.

Both Roche and UCB assume that it is possible that treatment be discontinued after 3 rather than 6 months through lack of efficacy.

6.2.8.1 AbbVie

The cost of all drugs used in the AbbVie analyses was calculated based on the recommended dosages and vial prices given in the Monthly Index of Medical Specialties 2013. Importantly the impact to the NHS of Patient Access Schemes (PAS) on the cost of certain drugs was not taken into account in the analysis, with AbbVie citing the NICE Methods Guide[194] states that PAS are valid until NICE technology appraisal review, at which point manufacturers will need to agree a new PAS (even if it's the same) in the current appraisal. As such, it is not known if all the current PAS in existence will be agreed again by PASLU and this is why they have not been included in the analysis. No sensitivity analyses were conducted using existing patient access schemes. This is unfavourable to: certolizumab pegol, where the initial 10 doses are provided free; abatacept and tocilizumab, where academic-in-confidence discounts are provided; and golimumab who provide the 100-mg dose of golimumab at the same price as the 50-mg dose.

AbbVie provide detailed breakdown of all conventional DMARDs and biologic treatments and do take patient weight into consideration. Abatacept sc is not considered. The cost per dose for biologic treatments assumed by AbbVie is reproduced in Table 94.

Table 94: The costs of bDMARDs assumed by AbbVie

Treatment	Dose regimen	Cost per dose
Adalimumab	40 mg; every other week	£352.14
Etanercept	50 mg; every week	£178.75
Infliximab	3 mg/kg: 0, 2, 6 then every 8 weeks	£1,133.28
Abatacept	500 mg below 60 kg, 750 mg between 60-100 kg, 1000 mg above 100 kg; 0, 2 and 4 weeks then every 4 weeks thereafter	£856.27
Rituximab	1000 mg followed by 1000 mg 2 weeks later repeated every 9 months	£1,746.30
Golimumab	50 mg below 100 kg, 100 mg above 100 kg, per month	£832.09
Tocilizumab	8 mg/kg every four weeks	£782.67
Certolizumab	400 mg, repeated 2 weeks and 4 weeks after initial injection	£715.00
Certolizumab	200 mg repeated every 2 weeks thereafter	£357.50

For interventions that are weight dependent AbbVie examined the weight distribution of patients enrolled in the BSRBR from the adalimumab cohort (N=4,364 patients) to determine the most likely average annual drug acquisition cost of tocilizumab, abatacept, infliximab and golimumab in the UK.

Tables 95 to 98 show the calculations undertaken by AbbVie to establish average cost per dose

Table 95: The calculation undertaken by AbbVie to establish the average expected cost per tocilizumab treatment

Possible combinations of tocilizumab vials	Total dose (mg)	Lower weight (kg)	Upper weight (kg)	Cost per dose	% patients in BSRBR	Annual cost
80+80+80	240	-	30	£307.20	0.05%	£3,993.60
200+80	280	31	35	£358.40	0.18%	£4,659.20
200+80+80	360	36	45	£460.80	1.67%	£5,990.40
400	400	46	50	£512.00	3.94%	£6,656.00
400+80	480	51	60	£614.40	18.42%	£7,987.20
400+80+80	560	61	70	£716.80	23.97%	£9,318.40
400+200	600	71	75	£768.00	11.07%	£9,984.00
400+200+80	680	76	85	£870.40	17.42%	£11,315.20
400+200+80+80	760	86	95	£972.80	11.73%	£12,646.40
400+400	800	96	-	£1,024.00	11.55%	£13,312.00
Average cost per dose				£782.67		
Average cost per year (13 doses)						**£10,174.65**

Table 96: The calculation undertaken by AbbVie to establish the average expected cost per abatacept treatment

Number of vials	Lower weight (kg)	Upper weight (kg)	Cost per dose	% patients in BSRBR	Annual cost (1st year)	Annual cost (2nd year and beyond)
2	-	60	£604.80	24.27%	£8,467.20	£7,862.40
3	61	100	£907.20	68.31%	£12,700.80	£11,793.60
4	36	45	£1,209.60	7.42%	£16,934.40	£15,724.80
Average cost per dose			£856.27			
Average cost per year (14 doses in the first year, 13 doses for year 2 and beyond)					**£11,987.76**	**£11,131.49**

Table 97: The calculation undertaken by AbbVie to establish the average expected cost per infliximab treatment

Number of vials	Lower weight (kg)	Upper weight (kg)	Cost per dose	% patients in BSRBR	Annual cost (1st year)	Annual cost (2nd year and beyond)
1	-	33	£419.62	0.14%	£3,356.96	£2,727.53
2	34	66	£839.24	38.13%	£6,713.92	£5,455.06
3	67	99	£1,258.86	54.31%	£10,070.88	£8,182.59
4	100	133	£1,678.48	6.58%	£13,427.84	£10,910.12
5	134	166	£2,098.10	0.64%	£16,784.80	£13,637.65
6	167	-	£2,517.72	0.21%	£20,141.76	£16,365.18
Average cost per dose			£1,133.28			
Average cost per year (8 doses in the first year, 6.5 doses on average for year 2 and beyond)					**£9,066.25**	**£7,366.33**

Table 98: The calculation undertaken by AbbVie to establish the average expected cost per golimumab treatment

Number of pens	Lower weight (kg)	Upper weight (kg)	Cost per dose	% patients in BSRBR	Annual cost
1	-	100	£774.58	92.58%	£9,294.96
2	101	-	£1,549.16	7.42%	£18,589.92
Average cost per dose			£832.09		
Average cost per year (12 doses)					**£11,649.23**

6.2.8.2 BMS

BMS estimate the yearly costs of each intervention and additional costs incurred in the first year due to loading doses. BMS assume that all patients weight 70kg, the lack of uncertainty in this value will likely favour those interventions that are weight based, and in particular tocilizumab. BMS consider PAS in place at the start of the appraisal, two of which, for tocilizumab and for both abatacept formulations are commercial-in-confidence. The bDMARDs costs assumed by BMS are replicated in Table 99.

Table 99: The intervention costs assumed by BMS

Treatment	Annual cost	Year 1 Start-up cost
IV abatacept	[redacted]	[redacted]
SC abatacept	[redacted]	[redacted]
Adalimumab	£9,187	£0
Etanercept	£9,327	£0
Infliximab	£8,211	£1,259
Tocilizumab	[redacted]	[redacted]
Golimumab	£9,156	£0
Certolizumab pegol	£9,327	-£2,503*
Rituximab	£4,817	£0
Leflunomide	£747	£0
Injectable gold	£135	£225
Cyclosporin A	£1,685	£0
Azathioprine	£98	£0
MTX	£18	£0

** The year 1 additional cost for certolizumab pegol is negative due to the free doses in the PAS. However, patients receive certolizumab pegol for a minimum of 6 months, so the cost is always positive. IV: intravenous; SC: subcutaneous.*

6.2.8.3 MSD

MSD have distinguished between the costs in the first 6 months, where loading doses may be needed, and costs in following six month cycles. These are replicated in Table 100. The PAS for certolizumab pegol and golimumab have been applied, but neither the tocilizumab nor the abatacept PASs (which are commercial-in-confidence) are used.

Table 100: The intervention costs assumed by MSD

	Cost per dose	No. doses per first 6 months	No. doses post 6 months	Treatment cost first 6 months	Treatment cost post 6 months
Golimumab	£762.97	6	6	£4,577.82	£4,577.82
Adalimumab	£352.14	13	13	£4,577.82	£4,577.82
Infliximab[A]	£1,133.20	5	3.25	£5,666.00	£3,682.90
Etanercept	£89.38	52	52	£4,647.76	£4,647.76
Tocilizumab[B]	£698.32	7	6.5	£4,888.24	£4,539.08
Certolizumab[C]	£357.50	6	13	£2,145.00	£4,647.50
Leflunomide	£1.88	205	178	£385.40	£334.64
Gold	£13.48	26	26	£350.48	£350.48
Azathioprine	£0.07	547.5	547.5	£38.33	£38.33
ciclosporin	£2.14	365	365	£781.10	£781.10
MTX	£0.05	78	78	£3.90	£3.90
Abatacept IV[D]	£864.92	8	6.5	£6,919.35	£5,621.97
Abatacept SC[E]	£302.40	26	26	£8,727.32	£7,862.40
Rituximab	£1,746.30	2	1.3	£3,492.60	£2,270.19

(A) average 2.70 vials with wastage; (B) average cost per infusion £887.32 with wastage; (C) includes PAS; (D) includes average 2.86 vials with wastage; (E) includes IV loading dose

The costs for weight based doses were calculated based on the weight distributions of 2,775 infliximab patients within the BSRBR database to estimate the average number of *full* vials that are used per patient (or in the case of tocilizumab the weighted average cost per patient). These data are shown in Table 101. 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.

Table 101: The number of vials assumed by MSD for weight based interventions

	0-33 kg	34-59 kg	60-66 kg	67-100 kg	101-133 kg	>134 kg (Max weight 174)	∑
Number in each infliximab weight group	2	574	465	1,546	176	12	2,775
Percentage in each group	0.07%	20.68%	16.76%	55.71%	6.34%	0.43%	100%
Infliximab vials per group (3 mg/kg)	1	2	2	3	4	6	-
Abatacept IV vials per group	2	2	3	3	4	4	-
Tocilizumab vials per group (8 mg/kg)	200 mg + 80mg	400 mg + 80 mg	400 mg + 80 mg + 80mg	400 mg + 400 mg	400 mg + 400 mg	400 mg + 400 mg	-
Cost per patient per weight group	£358.40	£614.40	£716.80	£1,024.00	£1,024.00	£1,024.00	
Weighted average infliximab vials per infusion: 2.70							
Weighted average abatacept IV vials per infusion: 2.86							
Weighted average tocilizumab cost per infusion: £887.32							

As an example, the calculation for the weighted average vials of infliximab is as follows:

$$(0.07\% * 1) + (20.68\% * 2) + (16.76\% * 2) + (55.71\% * 3) + (6.34\% * 4) + (0.43\% * 6) = 2.70$$

6.2.8.4 Pfizer

Drug costs in the Pfizer submission were taken from publicly available sources including patient access schemes for certolizumab pegol and golimumab. Patient access schemes which are not in the public domain, such as those for tocilizumab, abatacept iv and abatacept sc were not included.

For therapies administered based on the individual's weight, costs were calculated for each patient individually, and vial-wastage was permitted.

Palliative care was assumed to consist of a combination of MTX, leflunomide and ciclosporin. This was assumed to represent a proxy for the cost of treatment in this line of therapy given the heterogeneous nature of treatments that are likely to be given at this stage, in order, to try and control disease progression. Costs at this line of therapy are likely to be extremely heterogeneous and no accurate cost estimate was available, however given that patients reach palliative care after several lines of therapy, potentially taking many years, the effect of discounting will be to make this assumption less influential.

Where applicable (in for example the severe DMARD-IR (monotherapy) population), the cost of the generic 'cDMARD' therapy was assumed to have the cost of MTX. Again, the cost was intended to act as a proxy for a generic therapy of this class in the absence of a definitive patient pathway. This is likely to be a conservative estimation given that MTX is the one of the cheapest cDMARDs available. A summary of the drug costs with dosing assumptions is provided in Table 102.

Table 102: The intervention costs assumed by Pfizer

Tx	Dosing assumptions	Unit cost¶	Unit dose (mg)
ABT	Body-weight <60kg, 500mg, 50–100kg, 750mg, > 100kg, 100mg repeated 2 wks and 4 wks after initial infusion, then every 4 wks (291)	£302.40	250
ADA	40 mg every other wk (291)	£352.14	40
CZP	400 mg 0, 2 and 4 wks then 200 mg every 2 wks (PAS 10 for free) (291)	£357.50	200
CIC	Max of 4 mg/kg daily in 2 divided doses (291)	£51.50	3000
ETN	25 mg BIW (291)	£89.38	25
ABS	Loading dose by IV initially, then first 125 mg sc injection given within a day, followed by 125 mg sc OW.(294, 295)	£302.40††	125
GOL	50 mg every 4 wks (291)	£762.97	50
INF	3 mg/kg wk 0, 2 and 6 thereafter every 8 wks (294)	£419.62	100
LEF	Assumed 20mg OD	£61.36	600
MTX	15 mg OW (291)	£48.44	1000
PC	Assumed to be additive combination of MTX, LEF, CIC (oral)	NA	NA
RTX	1000 mg repeated two wks after initial infusion=1 course; each course 9 months apart (291)	£873.15	500
SUL	2000 mg/day (291)	£14.83	56000
TOC	8mg/kg every 4 wks (291)	£102.40	80
Comb cDMARD	Assumed to be additive combination of MTX and SUL	NA	NA

Abbreviations: ABT, abatacept (iv); ABS, abatacept subcutaneous; BIW, twice weekly; cDMARD, conventional disease modifying antirheumatic drug; CIC, ciclosporin; comb cDMARD, combination therapy with cDMARDs; ETN, etanercept; GOL, golimumab; INF, infliximab; iv, intravenous; LEF, leflunomide; max, maximum; MTX, MTX; OD, once daily; OW, once weekly; PAS, patient-access scheme; PC, palliative care; RTX, rituximab; sc, subcutaneous; Tx, treatment; SUL, sulfasalazine; TOC, tocilizumab. †Uplifted from costs presented by Roche in TA198 (111) to 2011/12 prices using Curtis, 2012 (293);‡ One hour community nurse time from Curtis, 2012 (293);§ 2 * day case cost for HD23C Inflammatory Spine, Joint or Connective Tissue Disorders, without CC (296); ¶ BNF 64 (291);†† BNF January 2013 (295); ‡‡model includes cost of iv loading dose – assumed to be the same as first administration of ABT and applied at the start of the strategy; §§Because the dose for RTX is 1000 mg and unit size is 500 mg, there was no vial wastage required.

6.2.8.5 Roche

The Roche submission only considered the use of tocilizumab in patients who are intolerant or contraindicated to MTX. It was assumed that all patients weigh 70kg although this was altered to 65kg and 75kg in sensitivity analyses. Table 103 presents the costs assumed by Roche, although it is

noted that Table 103 does not include the patient access scheme for tocilizumab that is used within the mathematical model. It is commented that it has been assumed that non-responders would be removed from treatment at 3 months which may underestimate the acquisition costs of treatments.

Table 103: The intervention costs assumed by Roche

			Cost for first 6 months		Cost per subsequent cycle
Treatment	Dose regimen*	Unit cost**	**Non-responders**	**Responders**	**Responders**
ADA	40mg every 2 weeks	£352.14 per 40mg vial	£2,289	£4,578	£4,578
CTZ	200mg every 2 weeks	£357.50 per 200mg syringe	£0	£2,324	£4,646
ETA	50mg every week	£178.75 per 50mg syringe	£2,324	£4,648	£4,648
TCZ	8mg/kg every 4 weeks	£1.28 per mg	£2,330	£4,659	£4,659

*Source for dose regimen: [The Electronic Medicines Compendium, 2011]

**Source for unit cost: [British National Formulary 2011]

6.2.8.6 UCB

The costs of drug acquisition were based on the recommended dosing schedules for treatment multiplied by the unit cost of treatment as reported in the British National Formulary 64 (2012[29]). The PASs for certolizumab pegol and golimumab were included but the commercial-in-confidence PASs for abatacept and tocilizumab were not incorporated

For IV drugs that are administered based on body weight (abatacept, infliximab, tocilizumab, azathioprine and cyclosporine), the weight distribution of patients enrolled to either the RAPID 1, RAPID 2 and FAST4WARD trials (severe disease activity population) or the CERTAIN study (moderate disease activity population) was applied to estimate the number of vials used.

For drugs that require loading doses or irregular administration, various assumptions were made to estimate the dose received by patients during the first and subsequent 6 months of treatment:

- For abatacept, it was assumed that during the first 6 months, treatment was administered at weeks 0, 2, 4, 8, 12, 16, 20 and 24, equating to 8 administrations. During the subsequent 6 months, it was assumed that administrations occurred at a frequency of every 4 weeks, equating to 6.5 administrations over a 26-week cycle.
- For infliximab, similar assumptions were made when estimating dosing, where treatment was administered at weeks 0, 2, 6, 14, and 22 during the first 6 months, and an average of 3.25 administrations during any subsequent 6-month period.
- For CZP, treatment was administered at weeks 0, 2 and 4 during the first month of treatment, with further doses administered every two weeks on a continuous basis until cessation.

A summary of the acquisition costs assumed by UCB is provided in Table 104

Table 104: The intervention costs assumed by UCB

Treatment	First 6 months Acquisition costs	Every 6 months thereafter Acquisition costs
Combination treatments with MTX (severe disease activity population)		
Certolizumab pegol + MTX	£2,163	£4,666
Abatacept + MTX	£7,005	£5,695
Infliximab + MTX	£5,648	£3,677
Tocilizumab + MTX	£6,475	£6,475
Adalimumab + MTX	£4,596	£4,596
Etanercept + MTX	£4,666	£4,666
Golimumab + MTX	£4,596	£4,596
Monotherapies (severe disease activity population)		
Certolizumab pegol	£2,145	£4,648
Tocilizumab	£6,457	£6,457
Adalimumab	£4,578	£4,578
Etanercept	£4,648	£4,648
Combination treatments (moderate disease activity population)		
Certolizumab pegol + MTX	£2,163	£4,666
Certolizumab pegol + cDMARDs	£2,255	£4,758
Placebo + MTX	£18	£18
Placebo + cDMARDs	£111	£111

6.2.9 Administration and monitoring costs

This section details the administration and monitoring costs assumed within the manufacturers' submission. Many submissions provide detailed descriptions with multiple tables to support the monitoring costs used. These have been abridged within this summary for brevity. In summary the monitoring costs are broadly comparable, and are unlikely to have a big impact on the conclusions of the cost-effectiveness analyses. The costs of infusion were typically between £100 and £200 per infusion in the submissions, although AbbVie use a value of £501 per infusion. Some submissions have costs associated with subcutaneous injections.

It is commented that in a recent NICE review (TA247[195]) the Appraisal Committee agreed that the value of £154 per infusion was 'acceptable'. No comment was made on the manufacturer's assumption that 10% of subcutaneous injections would require administration by a district nurse.

6.2.9.1 AbbVie

Administration costs of £501.48 were assumed in the AbbVie submission for each intravenous treatment, using data from NHS Reference Costs[196] and weighting the unit cost per day case admission (91%) and outpatient admission (9%) by activity levels. This assumption is based on the approach used in the NICE guidance for the use of infliximab for treatment of adults with psoriasis.[197] An administration cost of 416.12 corresponding to the cost of an outpatient visit was tested in the scenario analysis.[198]

Monitoring requirements have been modelled based on UK practice based on share care guidelines and monitoring protocols for rheumatology patients in Bradford teaching hospitals[198] as detailed in Table 105 and validated by clinical experts prior to the previous NICE submission. Monitoring costs were not applied for abatacept, infliximab, rituximab or tocilizumab to avoid double-counting as 91% of patients are assumed to be admitted as a day case at each administration and the laboratory tests are included in the tariff. The monitoring requirements are however presented in Table 106 for completeness.

In the model, costs of monitoring/lab tests required at baseline are applied once the patients start the treatment. Additionally, the scheduled monitoring required in 12 months are applied as a daily cost during the treatment duration. Unit costs for monitoring were taken from published sources and are displayed in Table 104.

Monitoring costs at baseline and for subsequent 12 months are presented in Table 105 and Table 106, respectively.

AbbVie report that "As per the guidelines it was assumed that any monitoring or lab tests in the first three months would be done by a specialist nurse and a shared care arrangement made with general practitioners (GPs) thereafter with routine clinic follow-up on a regular basis. We assumed that a health care visit was associated with each sequence of laboratory tests. Monitoring subsequently to the first three months was assumed to occur at a primary care setting in 60%–70% of cases as advised by experts, with the remainder of monitoring being carried out at a hospital. To calculate the distribution of visits the total number of visits beyond the first three months was multiplied by 65% and rounded to the closest integer to obtain the number of GP visits. For annual monitoring beyond six months, where the number of health care visits was calculated to be below four, equal distribution between primary and secondary care settings was used to account for regular clinic attendances.

Protocols were not available for golimumab, thus, the same monitoring pattern as for adalimumab was assumed. For combination therapies the maximum requirement for each test from the respective therapies was assumed.

"Monitoring costs are set to zero for rescue therapy, apart from an outpatient visit cost every two months as advised by clinical experts. These experts further advised that patients on rescue therapy would be subject to one inpatient admission of approximately three weeks annually. This was not included as additional resource use to avoid double-counting with HAQ-based inpatient and surgery costs. Rescue therapy refers to medical treatment once all active therapies, including traditional DMARDs and biologic treatments, have failed; and is assumed to consist of MTX."

Table 105: Monitoring costs assumed by AbbVie in the first six months

Test	Unit cost	MTX/ MTX+HCQ+SSZ	SSZ/LEF	CYC	HCQ	ADA/ETN/ CTZ/GOL Mono or Combination with MTX	Rescue
CXR	£29.33	1	0	0	0	1	0
FBC	£3.39	8	8	9	1	9	0
U& E	£6.36	8	8	9	1	9	0
LFT	£8.91	8	8	9	1	9	0
CRP	£8.49	8	8	9	1	8	0
Urinalysis	£7.84	0	0	1	0	1	0
Mantoux test	£16.34	0	0	0	0	1	0
Hepatitis serology	£7.84	0	0	0	0	1	0
ANA	£8.49	0	0	0	0	3	0
DNA	£8.49	0	0	0	0	1	0
Uric acid	£1.27	0	0	3	0	0	0
Lipids	£3.82	0	0	3	0	0	0
GP visit	£36.36	3	3	3	0	3	0
Outpatient visit	£132.75	5	5	6	1	6	3
Total		1019.36	990.03	1173.04	159.9	1236.75	398.25

ADA = adalimumab; ANA = antinuclear antibody; CRP = C-reactive protein; CTZ = certolizumab; CXR = chest x-ray; CYC = ciclosporin; DNA = deoxyribonucleic acid; ETN = etanercept; FBC = full blood count; GOL = golimumab; GP = general practitioner; HCQ = hydroxychloroquine; LEF = leflunomide; LFT = liver function test; MTX = MTX; SSZ = sulfasalazine; U&E = urea & electrolytes

Source: Bradford teaching hospitals July 2010[198], NHS reference costs 2010-2011,[196] NICE (CG33) Tuberculosis costing template,[199] PSSRU 2011.[200]

Table 106: Annual monitoring costs assumed by AbbVie after the first six months

Test	Unit cost	MTX/LEF, SSZ/MTX+HCQ+SSZ	ADA/ETN/CTZ/ GOL/monotherapy or combination	CYC	HCQ	Rescue
CXR	£29.33	0	0	0	0	0
FBC	£3.39	4	4	4	2	0
U& E	£6.36	4	4	4	2	0
LFT	£8.91	4	4	4	2	0
CRP	£8.49	4	4	4	2	0
ANA	£8.49	0	4	0	0	0
Uric acid	£1.27	0	0	4	0	0
Lipids	£3.82	0	0	4	0	0
GP visit	£36.36	2	2	2	1	0
Outpatient visit	£132.75	2	2	2	1	6
Total		**446.82**	**480.78**	**467.18**	**223.41**	**796.5**

ADA = adalimumab; ANA = antinuclear antibody; CRP = C-reactive protein; CTZ = certolizumab; CXR = chest x-ray; CYC = ciclosporin; ETN = etanercept; FBC = full blood count; GOL = golimumab; GP = general practitioner; HCQ = hydroxychloroquine; LEF = leflunomide; LFT = liver function test; MTX = MTX; SSZ = sulfasalazine; U&E = urea & electrolytes
Source: Bradford teaching hospitals July 2010,[198] NICE (CG33) Tuberculosis costing template,[199] PSSRU 2011[200]

AbbVie acknowledge that monitoring protocols from the British Society of Rheumatology (BSR) would be more representative to the population modelled, rather than regional guidelines detailed in the Bradford Primary Care Trust protocols. As monitoring patterns from the BSR[201] are not detailed for biologic therapies, the Bradford protocols were used in the base case as all relevant comparators were included, thus, allowing for consistent costing of monitoring patterns without the requirement of further assumptions. AbbVie demonstrate the total costs of monitoring for DMARDs between the two sources were reasonably comparable with slightly higher estimates obtained using Bradford protocols. Alternative monitoring patterns from the BSR, assuming the same monitoring pattern as that of MTX for biologic arms were tested in scenario analysis. In addition the sensitivity of monitoring costs was tested by increasing the total monitoring costs for each comparator by 50%.

6.2.9.2 BMS

Infliximab, abatacept iv, and tocilizumab are administered as infusions, with subcutaneous treatments assumed to require visits to a nurse specialist in year 1.[202] Treatment with injectable gold requires a visit to a general practitioner (GP) for each dose. The annual and year 1 administration costs are shown in Table 107. BMS assume that cDMARDs and tocilizumab require tests before and during treatment. The annual monitoring costs assumed by BMS are shown in Table 107.

Table 107: The administration costs and monitoring costs assumed by BMS

	Administration Costs		Monitoring Costs	
Treatment	**Annual cost**	**Year 1 additional cost**	**Annual cost**	**Year 1 additional cost**
IV abatacept	£1,777	£136	£0	£0
SC abatacept	£0	£283	£0	£0
Adalimumab	£0	£147	£0	£0
Etanercept	£0	£147	£0	£0
Infliximab	£888	£136	£0	£0
Tocilizumab	£1,777	£0	£557	£554
Golimumab	£0	£147	£0	£0
Certolizumab pegol	£0	£147	£0	£0
Rituximab	£188	£0	£0	£0
Leflunomide	£0	£0	£854	£1,263
Injectable gold	£516	£860	£1,710	£2,849
Cyclosporin A	£0	£0	£1,671	£1,127
Azathioprine	£0	£0	£1,709	£854
MTX	£0	£0	£1,709	£570
			£545	£0

IV: intravenous; SC: subcutaneous.

BMS present a combined intervention acquisition, administration and monitoring costs. All of the biologic treatments are co-prescribed with MTX, so include the annual costs for MTX treatment. The additional year 1 costs for MTX are included only once in the model, as it is assumed that patients move straight onto the next biologic treatment and so do not cease and re-start treatment with MTX. These values are replicated in Table 108.

Table 108: Summarised total and annual costs assumed by BMS

Treatment	Annual cost	Start-up cost
IV abatacept	[redacted]	[redacted]
SC abatacept	[redacted]	[redacted]
Adalimumab	£10,913.92	£147.00
Etanercept	£11,053.76	£147.00
Infliximab	£10,825.87	£1,395.06
Tocilizumab	[redacted]	[redacted]
Golimumab	£10,882.48	£147.00
Certolizumab pegol	£11,053.76	-£2,355.50*
Rituximab	£6,732.08	£0.00
Leflunomide	£1,601.34	£1,408.44
Injectable gold	£2,360.40	£4,079.56
Cyclosporin A	£3,356.35	£1,275.33
Azathioprine	£1,806.55	£999.75
Palliative care	£544.80	£0.00
MTX		£733.48

** The year 1 additional cost for certolizumab pegol is negative due to drug costs (the free doses in the PAS). However, patients receive certolizumab pegol for a minimum of 6 months, so the cost is always positive. All costs include cost of MTX.*
IV: intravenous; SC: subcutaneous.

6.2.9.3 MSD

MSD note that although many of the TNFα inhibitors are administered at home, patients are often initially taught how to administer treatment within a hospital. This is calculated as a one-off administration cost.

MSD report that the current clinical management of this condition requires patients to have a regular contact with the specialist rheumatology centres in the UK. This was estimated in consultation with two expert clinicians in the UK. Initial resource use estimates were made based on the assumptions made in the BRAM. These were reviewed and validated or changed by the clinical experts. Recent guidelines from the American College of Rheumatology and the British Society for Rheumatology were also reviewed for consistency with our assumptions.

In order to determine the total treatment cost in the model, routine monitoring costs of patients is aggregated. In the UK patient monitoring includes visits to a rheumatologist after 6 months then every 12 months, general practitioner visits every 6 months, and a specialist nurse visit every 6 months.

Resource use costs for the UK were sourced from the NHS reference costs (2010-2011), and the Personal Social Services Research Unit (2011). It is common in the UK for patients to regularly visit a specialist rheumatology nurse more frequently than their rheumatologist. Table 109 present the unit costs assumed by MSD.

Table 109: The unit costs of monitoring assumed by MSD

Healthcare resource	Unit cost	Source
Rheumatologist	132.07	NHS reference cost 2010-2011 (Consultant Led: Follow up Attendance Non-Admitted Face to Face 410)
General practitioner	53.00	PSSRU (2011) p.149
Specialist nurse	50.00	PSSRU (2011) p.144
Nurse practitioner	42.00	PSSRU (2011) p.146
Full blood count	3.36	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP823)
Erythrocyte sedimentation rate	1.26	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP841)
Biochemistry profile	3.36	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP823)
CRP	3.36	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP823)
TB test	1.26	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP841)
Hep B and Hep C	3.36	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP823)
Urinalysis	1.26	NHS reference cost 2010-2011 (NHS Trusts Direct Access: Pathology Services DAP841)
Chest X-ray	29.04	NHS reference cost 2010-2011 (NHS Trusts Outpatient DAPF)

For intravenous drugs (infliximab, tocilizumab, and abatacept iv) administration costs are higher and incurred at every administration of treatment. In the UK the cost of infusion is £50 with an additional £59 administration cost. The cost of infusion is assumed equivalent to a visit to a specialist nurse plus an hourly charge for the care of the patient whilst they are on the ward. MSD assumed that infusion costs can only be charged per whole hour.

In order to account for the difference in cost between initiation of treatment and maintenance treatment, the cost of the first cycle of treatment is aggregated separately to the cost of subsequent cycles of treatment. Table 110 reports the cost of administration treatment included in the model. As this was combined with intervention acquisition costs these have been included for completeness.

Table 110: The assumed administration, monitoring and drug acquisition costs assumed by MSD

	Cost per dose	No. doses per first 6 months	No. doses post 6 months	Treatment cost first 6 months	Treatment cost pot 6 months	Cost per administration first 6 months	Total cost first 6 months	Total cost post 6 months
Golimumab	£762.97	6	6	£4,577.82	£4,577.82	£59.00	£4,636.82	£4,577.82
Adalimumab	£352.14	13	13	£4,577.82	£4,577.82	£59.00	£4,636.82	£4,577.82
Infliximab[A]	£1,133.20	5	3.25	£5,666.00	£3,682.90	£109.00	£6,211.00	£4,037.15
Etanercept	£89.38	52	52	£4,647.76	£4,647.76	£59.00	£4,706.76	£4,647.76
Tocilizumab[B]	£698.32	7	6.5	£4,888.24	£4,539.08	£109.00	£5,651.24	£5,247.58
Certolizumab[C]	£357.50	6	13	£2,145.00	£4,647.50	£59.00	£2,204.00	£4,647.50
Leflunomide	£1.88	205	178	£385.40	£334.64	£0.00	£385.40	£334.64
Gold	£13.48	26	26	£350.48	£350.48	£0.00	£350.48	£350.48
Azathioprine	£0.07	547.5	547.5	£38.33	£38.33	£0.00	£38.33	£38.33
Ciclosporin	£2.14	365	365	£781.10	£781.10	£0.00	£781.10	£781.10
MTX	£0.05	78	78	£3.90	£3.90	£0.00	£3.90	£3.90
Abatacept IV[D]	£864.92	8	6.5	£6,919.35	£5,621.97	£109.00	£7,791.35	£6,330.47
Abatacept SC[E]	£302.40	26	26	£8,727.32	£7,862.40	£59.00	£8,895.32	£7,862.40
Rituximab	£1,746.30	2	1.3	£3,492.60	£2,270.19	£109.00	£3,710.60	£2,411.89

(A) average 2.70 vials with wastage; (B) average cost per infusion £887.32 with wastage; (C) includes PAS; (D) includes PAS and average 2.86 vials with wastage; (E) includes IV loading dose and associated administration cost

6.2.9.4 Pfizer

Pfizer assessed the costs of pre-treatment monitoring were included in the model as per previous evidence review group models and recent manufacturer's submission to NICE. These were reported to be then validated at an advisory board. In addition to the costs of tests, an outpatient rheumatology contact (service code 410) was assumed, at a cost of £137[203] Table 111 provides the unit costs of pre-treatment test whilst Table 112 summarises the estimated total cost per intervention. Monitoring costs were assumed to be included in the general costs per HAQ band and were thus not included.

The costs of infusion were Uplifted from costs presented by Roche in TA198[204] to 2011/12 prices using Curtis, 2012.[205]

Table 111: Unit costs of pre-treatment tests assumed by Pfizer

Test	Code	Cost	Source
Full blood count	FBC	£3.36	Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined . 2012. (Direct Access: Pathology Services, Haematology, DAP823)(296)
ESR	ESR	£3.36	Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined . 2012. (Direct Access: Pathology Services, Haematology, DAP823)(296)
Biochemical profile	BCP	£1.26	NHS Reference Costs 2011 (Direct Access: Pathology Services, Haematology, DAP841)
Chest x-ray	CXR	£19.17	Malottki et al. 2011(7) Uplifted to 2011/12 prices using Curtis 2012, assuming reported above were 2004/05 (293)
Urinalysis	URI	£1.26	Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined . 2012. (Direct Access: Pathology Services, Haematology, DAP841)(296)
Hep B & Hep C	HBC	£6.72	2 x NHS Reference Costs 2011 (Direct Access: Pathology Services, Haematology, DAP823)
Lipdid test	LIP	£3.36	Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined . 2012. (Direct Access: Pathology Services, Haematology, DAP823)(296)
C-reactive protein	CRP	£3.36	Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined . 2012. (Direct Access: Pathology Services, Haematology, DAP823)(296)
TB test	TB	£3.36	Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined . 2012. (Direct Access: Pathology Services, Haematology, DAP823)(296)

Table 112: Pre-treatment costs per intervention assumed by Pfizer

Treatment	Pre-treatment assumptions	Total cost
ABT, ABS†, ADA, CZP, ETN, GOL, IFX	FBC, ESR, BCP, CXR, CRP, TBT	£171
LEF	FBC, ESR, BCP, URI CRP	£150
PC	FBC, ESR, BCP, URI CRP	£168
MTX, combination cDMARD‡	FBC, ESR, BCP, CXR	£164
RTX	FBC, ESR, BCP, HBC, CXR, CRP, TBT	£178
SSZ	FBC, ESR, BCP	£145
TCZ	FBC, ESR, BCP, CXR, LIP, CRP, TBT	£174

Abbreviations: ABT, abatacept; ABS, abatacept subcutaneous; ADA, adalimumab;BCP, biochemical profile;cDMARD, conventional disease modifying antirheumatic drug; CRP, C-reactive protein; CXR, chest x-ray; CZP, certolizumab pegol;ETN, etanercept; FBC, full blood count; ESR, erythrocyte sedimentation rate; GOL, golimumab;HBC, Hep B&C; IFX, infliximab LEF, leflunomide; LIP, lipid test; MTX, MTX; PC, palliative care; RTX, rituximab; SSZL, sulfasalazine;TBT, TB test; TOC, tocilizumab; URI, urinalysis; †n Assumed to be the same as ABT in the absence of evidence; ‡ Assumed to be the same as MTX in the absence of evidence

The summary of acquisition costs, monitoring and administration costs provided by MSD is replicated in Table 113.

Table 113: The assumed acquisition and administration costs assumed by Pfizer

Tx	Dosing assumptions	Unit cost¶	Unit dose (mg)	Administration costs		Assume vial wastage?
				First administration	Subsequent administration	
ABT	Body-weight <60kg, 500mg, 50–100kg, 750mg, > 100kg, 100mg repeated 2 wks and 4 wks after initial infusion, then every 4 wks (291)	£302.40	250	£151.95†	£151.95†	YES
ADA	40 mg every other wk (291)	£352.14	40	£49.00‡	£0.00	NA
CZP	400 mg 0, 2 and 4 wks then 200 mg every 2 wks (PAS 10 for free) (291)	£357.50	200	£49.00‡	£0.00	NA
CIC	Max of 4 mg/kg daily in 2 divided doses (291)	£51.50	3000	£0.00	£0.00	NA
ETN	25 mg BIW (291)	£89.38	25	£49.00‡	£0.00	NA
ABS	Loading dose by IV initially, then first 125 mg sc injection given within a day, followed by 125 mg sc OW.(294, 295)	£302.40††	125	£49.00 (of sc first administration)‡‡	£0.00	NA
GOL	50 mg every 4 wks (291)	£762.97	50	£49.00‡	£0.00	NA
IFX	3 mg/kg wk 0, 2 and 6 thereafter every 8 wks (294)	£419.62	100	£151.95†	£151.95†	YES

Tx	Dosing assumptions	Unit cost¶	Unit dose (mg)	Administration costs		Assume vial wastage?
				First administration	Subsequent administration	
LEF	Assumed 20mg OD	£61.36	600	£0.00	£0.00	NA
MTX	15 mg OW (291)	£48.44	1000	£0.00	£0.00	NA
PC	Assumed to be additive combination of MTX, LEF, CIC (oral)	NA	NA	£0.00	£0.00	NA
RTX	1000 mg repeated two wks after initial infusion=1 course; each course 9 months apart (291)	£873.15	500	£441.00§	£441.00§	NA§§
SSZ	2000 mg/day (291)	£14.83	56000	£0.00	£0.00	NA
TCZ	8mg/kg every 4 wks (291)	£102.40	80	£151.95†	£151.95†	YES
Comb cDMARD	Assumed to be additive combination of MTX and SUL	NA	NA	£0.00	£0.00	NA

Abbreviations: ABT, abatacept (iv); ABS, abatacept subcutaneous; BIW, twice weekly; cDMARD, conventional disease modifying antirheumatic drug; CIC, ciclosporin; comb cDMARD, combination therapy with cDMARDs; ETN, etanercept; GOL, golimumab; INF, infliximab; iv, intravenous; LEF, leflunomide; max, maximum; MTX, MTX; OD, once daily; OW, once weekly; PAS, patient-access scheme; PC, palliative care; RTX, rituximab; sc, subcutaneous; Tx, treatment; SSZ, sulfasalazine; TCZ, tocilizumab. †Uplifted from costs presented by Roche in TA198 (111) to 2011/12 prices using Curtis, 2012 (293);‡ One hour community nurse time from Curtis, 2012 (293);§ 2 * day case cost for HD23C Inflammatory Spine, Joint or Connective Tissue Disorders, without CC (296); ¶ BNF 64 (291);†† BNF January 2013 (295); ‡‡model includes cost of iv loading dose – assumed to be the same as first administration of ABT and applied at the start of the strategy; §§Because the dose for RTX is 1000 mg and unit size is 500 mg, there was no vial wastage required.

6.2.9.5 Roche

Table 114 presents administration costs for all the treatments. The model assumes a district nurse will administer 10% of the subcutaneous injection treatments.

The economic model assumes the same schedule of monitoring for all biologics as in the previous NICE submission for TCZ (2011). The cost of tocilizumab monitoring is assumed to be included in the administration cost; £171.33 per IV infusion [Barton 2004[152]] updated to 2009/10 prices.[206]

Table 114: The administration costs assumed by Roche

Treatment	Total cost of administration first 6 months and subsequent cycles (responders)	Assumptions	Source (cost)
ADA	£35.10	10% of injections are given by district nurse; cost of district nurse: £27.00	Curtis 2010
CTZ	£35.10	10% of injections are given by district nurse; cost of district nurse: £27.00	Curtis 2010
ETA	£70.20	10% of injections are given by district nurse; cost of district nurse: £27.00	Curtis 2010
TCZ	£1,113.63	Cost of £171.33 for each infusion given in a cycle (inflated 2000 to 2010)	Barton 2004

The monitoring cost of adalimumab, certolizumab pegol and etanercept is assumed to follow the schedule presented in Table 115. Palliative care is assumed to have only monitoring costs but a greater number of outpatient follow up visits in the first cycle, and greater resource use in subsequent cycles resulting in costs of £2589 and subsequent costs of £1287

Table 115: The monitoring costs assumed by Roche for adalimumab, certolizumab pegol and etanercept

Resource or test	Unit Cost	Monitoring frequency per 6 months (first cycle)	Total cost (first cycle: responder)	Frequency of monitoring per 6 months (subsequent cycles)	Total cost (subsequent cycles)	Source
Outpatient visit first attendance	£214.00	1	£214.00	0	£0.00	Department of Health, 2011
Outpatient visit follow-up visit	£126.00	6	£756.00	3	£378.00	Department of Health, 2011
GP visit	£53.00	4	£212.00	3	£159.00	Department of Health, 2011
Full blood count	£3.00	14	£42.00	3	£9.00	Department of Health, 2011
Erythrocyte sedimentation and Creative protein	£15.41	14	£215.68	3	£46.22	Barton 2004
Liver function test	£8.55	14	£119.74	3	£25.66	Barton 2004
Urea, electrolytes and creatinine	£8.55	14	£119.74	3	£25.66	Barton 2004
Chest X-ray	£27.63	1	£27.63	0	£0.00	Barton 2004
Total			£1,706.79		£643.53	

Roche provide a summary table of acquisition, monitoring and administration costs. This is replicated in Table 116

Table 116: The total costs of treatment assumed by Roche

Treatment	Total cost: bi-annual (first cycle on treatment, non-responder)	Total cost: bi-annual (first cycle on treatment, responder)	Total cost: bi-annual (subsequent cycles on treatment, responder)
Adalimumab	£3,159.85	£6,319.71	£5,256.45
Certolizumab pegol	£870.94	£4,065.64	£5,326.13
Etanercept	£3,212.24	£6,424.49	£5,361.23
Tocilizumab	£2,886.42	£5,772.83	£5,772.83
Palliative care	£2,588.79	£2,588.79	£1,287.07

6.2.9.6 UCB

The monitoring schedule assumed by UCB is replicated in Table 117. UCB present unit costs, but for brevity only the summarised monitoring data, together with drug acquisition costs are provided in Table 117.

Table 117: Drug monitoring schedule: visits during first 6 months and every 6 months thereafter assumed by UCB

	First 6 months		Every 6 months thereafter	
	GP visit	Outpatient visit	GP visit	Outpatient visit
Certolizumab pegol	5	1	2	1
Certolizumab pegol + MTX	12	1	5	1
Abatacept	0	0	0	0
Abatacept + MTX (*)	0	0	0	0
Infliximab + MTX (*)	0	0	0	0
Rituximab + MTX (*)	0	0	0	0
Tocilizumab (*)	0	0	0	0
Tocilizumab + MTX (*)	0	0	0	0
Adalimumab	5	1	2	1
Adalimumab + MTX	12	1	5	1
Etanercept	5	1	2	1
Etanercept + MTX	12	1	5	1
Golimumab	5	1	2	1
Golimumab + MTX	12	1	5	1
Placebo + MTX	12	1	5	1
Azathioprine	12	1	5	1
Cyclosporine	8	1	5	1
Gold	23	1	8	1
Hydroxychloroquine	2	1	1	1
Leflunomide	12	1	3	1
Penicillamine	10.7	1	6	1
Sulfasalazine	7	1	1	1
Palliation	0	2	0	2
MTX + Sulfasalazine	12	1	5	1
MTX + Sulfasalazine + Hydroxychloroquine	12	1	5	1
MTX + Hydroxychloroquine	12	1	5	1
Hydroxychloroquine + Sulfasalazine	7	1	1	1
MTX + Leflunomide	12	1	5	1
MTX	12	1	5	1

Note: (*) cost of administration of treatment is assumed to cover healthcare visits for tests and monitoring

Table 118: Summary of drug acquisition, administration and monitoring costs for each treatment comparator in the model

	First 6 months				Every 6 months thereafter				First year
Treatment	**Acquisition costs**	**Administration costs**	**Monitoring costs**	**Total costs**	**Acquisition costs**	**Administration costs**	**Monitoring costs**	**Total costs**	**Total costs**
Combination treatments with MTX (severe disease activity population)									
Certolizumab pegol + MTX	£2,163	£45	£818	£3,026	£4,666	£0	£377	£5,043	£8,070
Abatacept + MTX	£7,005	£3,328	£101	£10,434	£5,695	£2,704	£34	£8,433	£18,868
Infliximab + MTX	£5,648	£2,080	£101	£7,829	£3,677	£1,352	£39	£5,068	£12,897
Tocilizumab + MTX	£6,475	£832	£101	£7,408	£6,475	£832	£34	£7,341	£14,749
Adalimumab + MTX	£4,596	£45	£818	£5,459	£4,596	£0	£377	£4,973	£10,433
Etanercept + MTX	£4,666	£45	£818	£5,529	£4,666	£0	£377	£5,043	£10,573
Golimumab + MTX	£4,596	£45	£818	£5,459	£4,596	£0	£377	£4,973	£10,433
Monotherapies (severe disease activity population)									
Certolizumab pegol	£2,145	£45	£491	£2,681	£4,648	£0	£230	£4,877	£7,559
Tocilizumab	£6,457	£832	£77	£7,366	£6,457	£832	£16	£7,304	£14,670
Adalimumab	£4,578	£45	£491	£5,114	£4,578	£0	£230	£4,808	£9,922
Etanercept	£4,648	£45	£491	£5,184	£4,648	£0	£230	£4,878	£10,062
Combination treatments (moderate disease activity population)									
Certolizumab pegol + MTX	£2,163	£45	£880	£3,088	£4,666	£0	£406	£5,071	£8,159
Certolizumab pegol + cDMARDs	£2,255	£45	£954	£3,254	£4,758	£0	£427	£5,185	£8,439
Placebo + MTX	£18	£0	£861	£879	£18	£0	£398	£417	£1,296
Placebo + cDMARDs	£111	£0	£935	£1,046	£111	£0	£412	£522	£1,568

Note: the costs for certolizumab pegol account for the patient access scheme agreed with the NHS; the cost of toclizumab and abatacept is based on the publically available list price as reported by the British National Formulary; therefore the reported cost does not take into account the confidential price discount patient access scheme agreed between the manufacturers and the Department of Health

6.2.10 Comparative treatment efficacy (Mixed Treatment Comparison / Network Meta Analysis)

This section contains the analyses regarding comparative efficacies undertaken by each manufacturer. The level of detail in the analyses and in the reporting was very diverse ranging from the submission by AbbVie which included a 378 page Appendix to the submission by Roche that consisted of one page concerning the MTC. The Assessment Group has attempted to capture all key points made by the manufacturer but has had, for brevity reasons, to abridge some analyses. Detailed discussions on the methods used, goodness of fits, consistency checking and convergence have not been incorporated. Similarly, replications of the list of studies that have been used in the MTC by the manufacturers have not been undertaken.

6.2.10.1AbbVie

The trials included in AbbVie's base case MTC are depicted in Figure 21 which have been taken from the AbbVie submission. The numbers on the line have been included by AbbVie without a reference, but are believed to represent codes for RCTs; thus 6 numbers would indicate six trials informing the direct comparison. It is commented that there is no cDMARD node which is assumed to be subsumed within the placebo arm.

AbbVie incorporated hurdles within the analyses to eliminate illogical results such as the possibility that a patient may be simulated an ACR50 response, but not an ACR20 response. This was achieved by using parameters such as for those that have gained an ACR20 response what proportion achieved an ACR50 response. Within the base case AbbVie adjusted for baseline risk, prior MTX exposure, prior biologic DMARD exposure and concomitant standard DMARD. AbbVie report that additional sensitivity analysis controlling for differences in baseline HAQ-DI and disease duration slightly worsened model fit assessed by the deviance information criterion and had little effect on overall results.

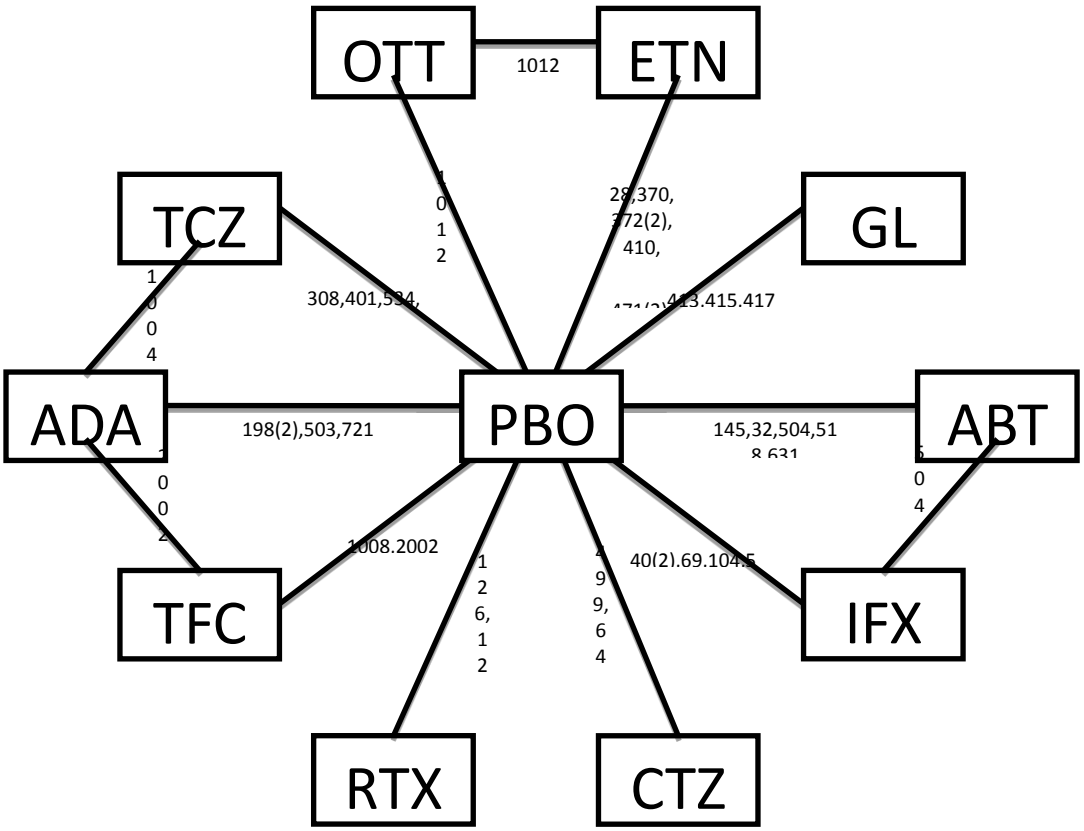
AbbVie present posterior simulated ACR responses for four main groups:

- MTX-experienced patients who can receive cDMARDs, (Figure 22)
- MTX-experienced patients who receive bDMARD monotherapy, (Figure 23)
- MTX-experienced patients who can receive cDMARDs, (Figure 24)
- MTX-experienced patients who receive bDMARD monotherapy, (Figure 25)

Further analyses (not shown in the Assessment Group summary) investigated a number of sensitivity analyses. These included

- The efficacy of tocilizumab and rituximab compared with MTX when used after a bDMARD. These results indicated that the efficacy of tocilizumab was lower following an initial bDMARD than in people who were bDMARD naïve.
- The inclusion of Asian studies which was shown to favour tocilizumab monotherapy and slightly favour certolizimub pegol.
- Limiting the data to a 3 month dataset. AbbVie comment that as one would expect, there are lower estimated median response probabilities at higher levels of response, particularly for ACR70 for most treatments including adalimumab, certolizumab, etanercept, golimumab and tocilizumab, compared to the "6 month" estimates. The only exceptions are abatacept and infliximab in the MTX-experienced, combination therapy scenario.

Figure 22: The evidence network in AbbVie's base case



Abbreviations: ADA – adalimumab; ABT – abatacept iv; CTZ – certolizumab pegol; ETN – etanercept; GLM – golimumab; IFX – infliximab; OTT – oral triple therapy; PBO – placebo; RTX – rituximab; TCZ – tocilizumab; TFC – tofacitinib

Figure 23: Posterior simulated ACR response for combination therapy in a MTX-experienced population presented by AbbVie

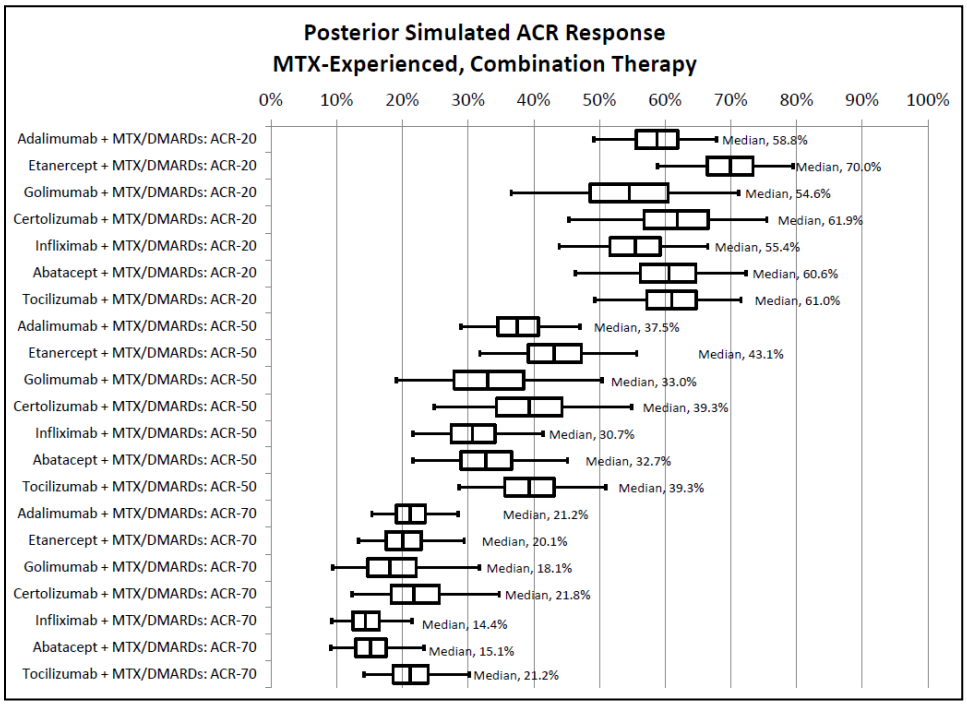


Figure 24: Posterior simulated ACR response for monotherapy in a MTX-experienced population presented by AbbVie

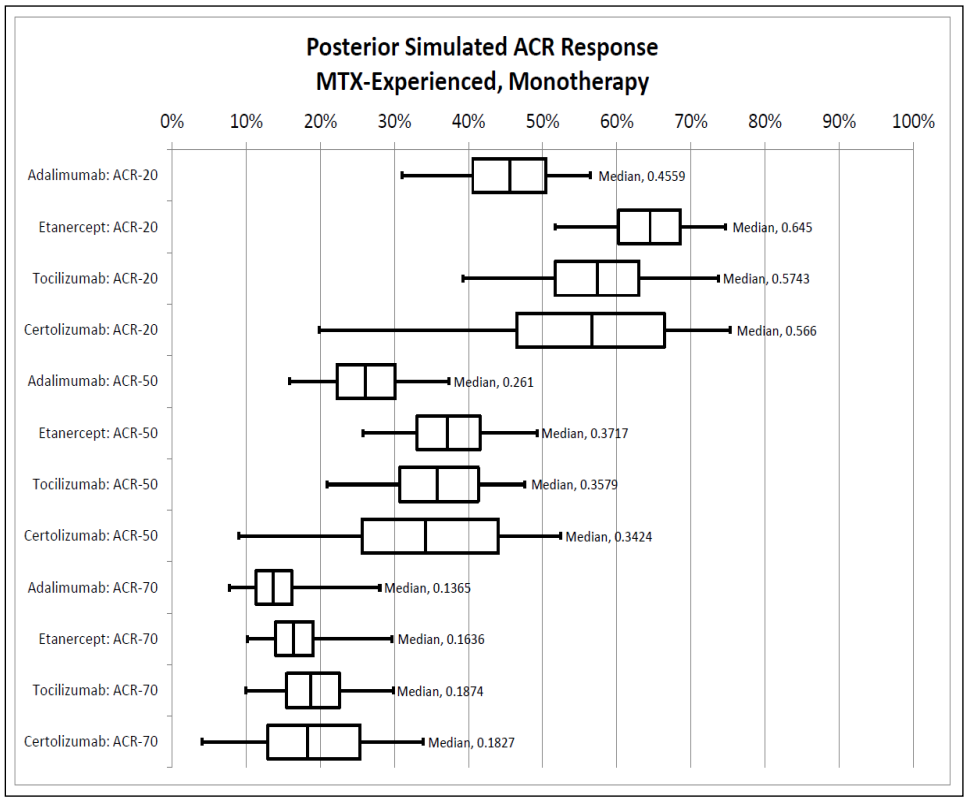


Figure 25: Posterior simulated ACR response for combination therapy in a MTX-naive population presented by AbbVie

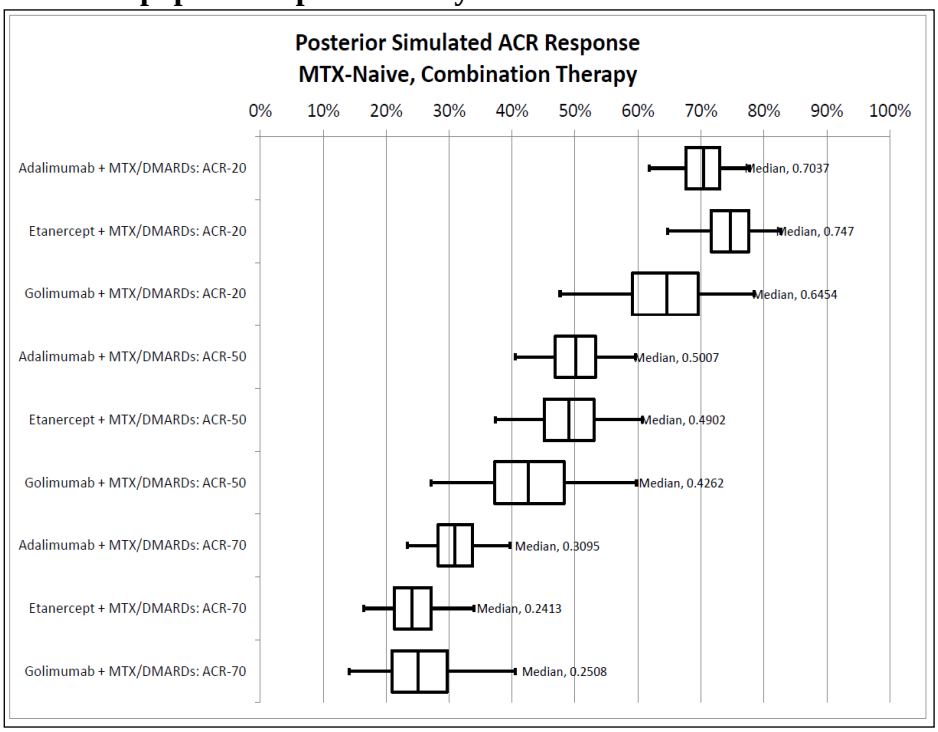
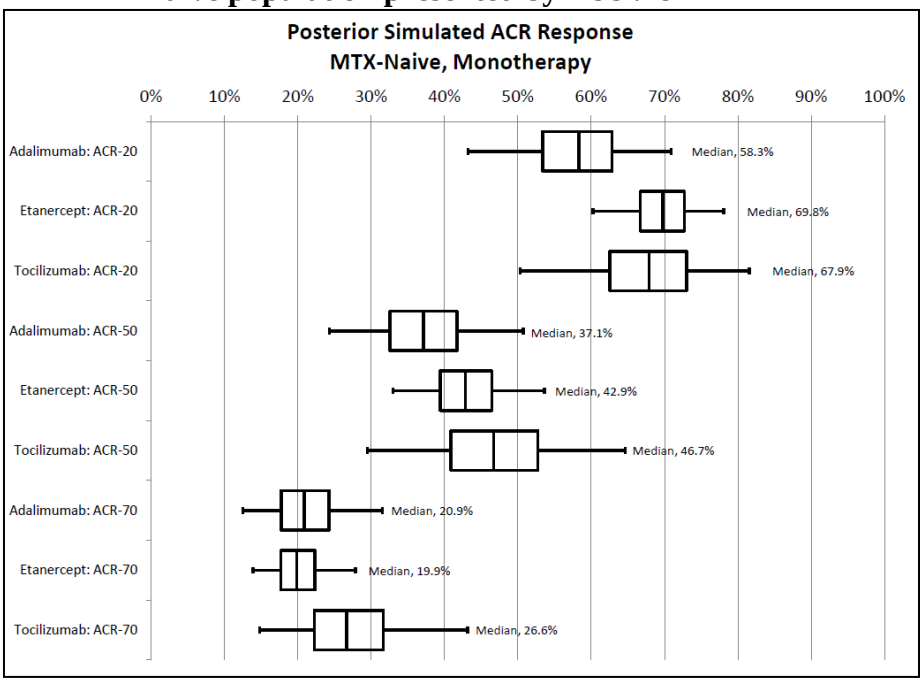


Figure 26: Posterior simulated ACR response for monotherapy in a MTX-naive population presented by AbbVie



AbbVie's interpretation of the MTC data

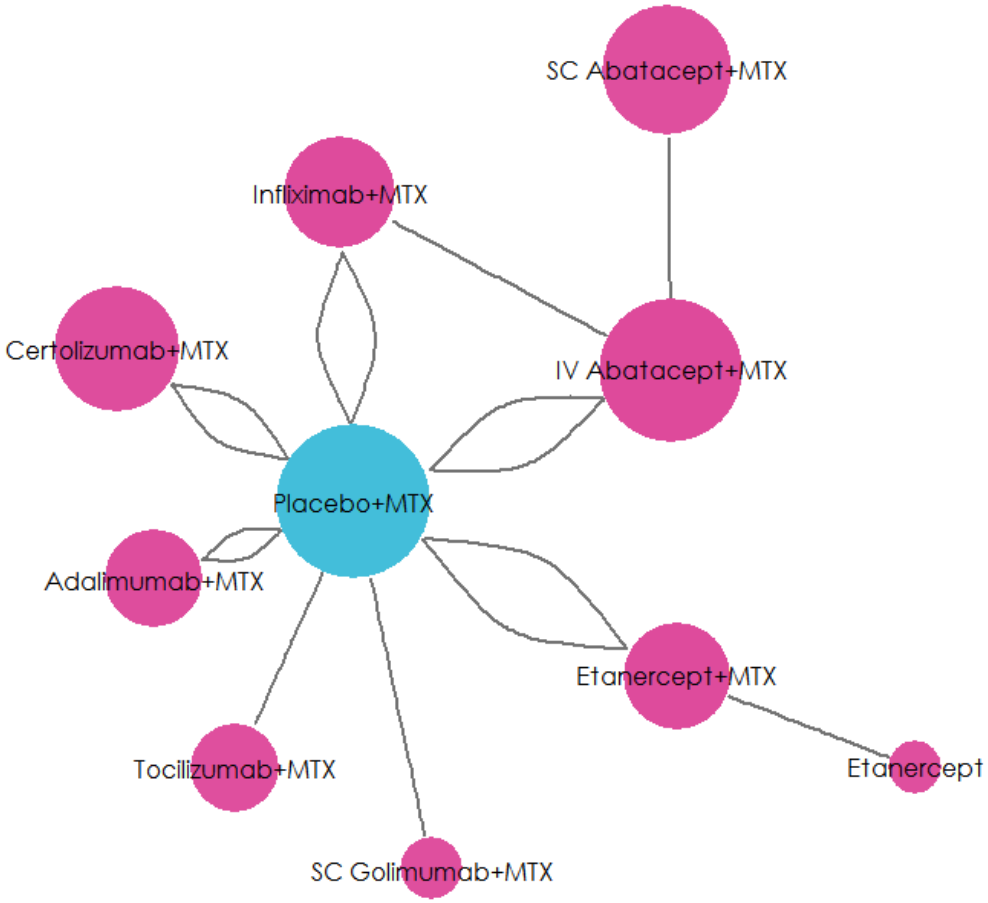
AbbVie state that "for the MTX-experienced patient population, biologics in combination with MTX or other DMARDs, median posterior simulated ACR20 responses for the 6 month estimates are

highest for etanercept and lowest for golimumab. The interquartile ranges are tighter for the three older anti-TNFs, adalimumab, etanercept and infliximab, as well as abatacept than for golimumab and certolizumab. Median posterior simulated ACR50 responses are highest for etanercept and lowest for infliximab, while ACR70 responses are highest for adalimumab and certolizumab and lowest for abatacept and infliximab. Estimated responses get tighter the higher the level of ACR response."

6.2.10.2BMS

The inclusion and exclusion criteria for selecting the RCTs to be evaluated in the MTC was not well-reported as were the time points at which data were extracted; the methods used within the MTC; the assumed properties of the frequentist and Bayesian analyses.BMS provide MTC analyses of HAQ scores and of DAS scores. The network for the HAQ scores are shown in Figure 27.

Figure 27: The network of evidence for HAQ scores as supplied by BMS



The mean change in HAQ shown in Figure 28 and absolute mean change shown in Figure 29.

Figure 28: The mean change in HAQ scores relative to placebo as estimated by BMS

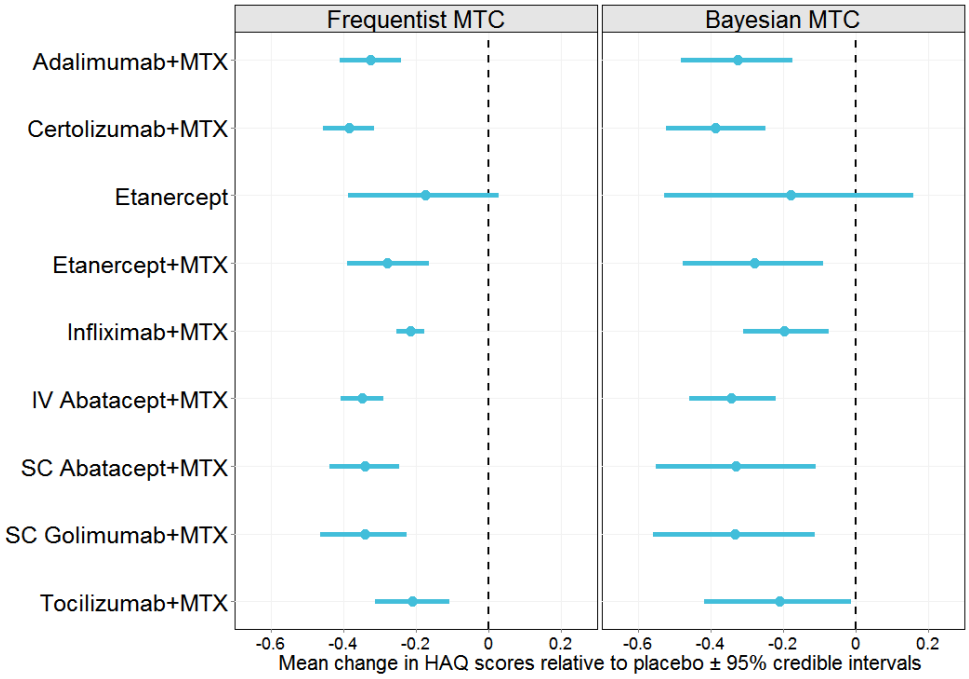
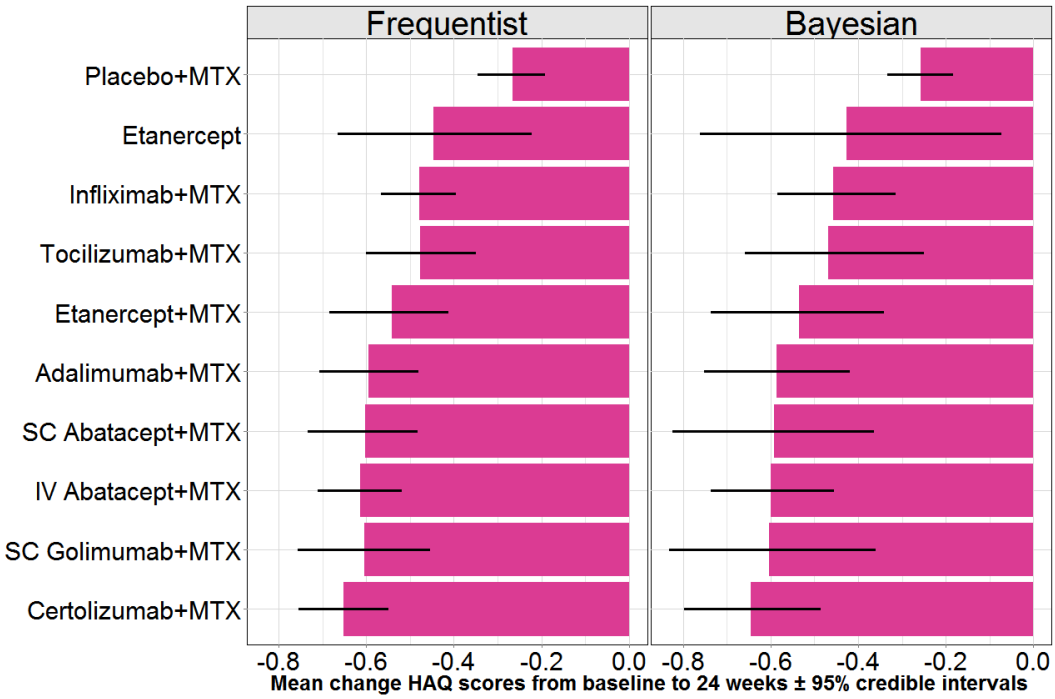
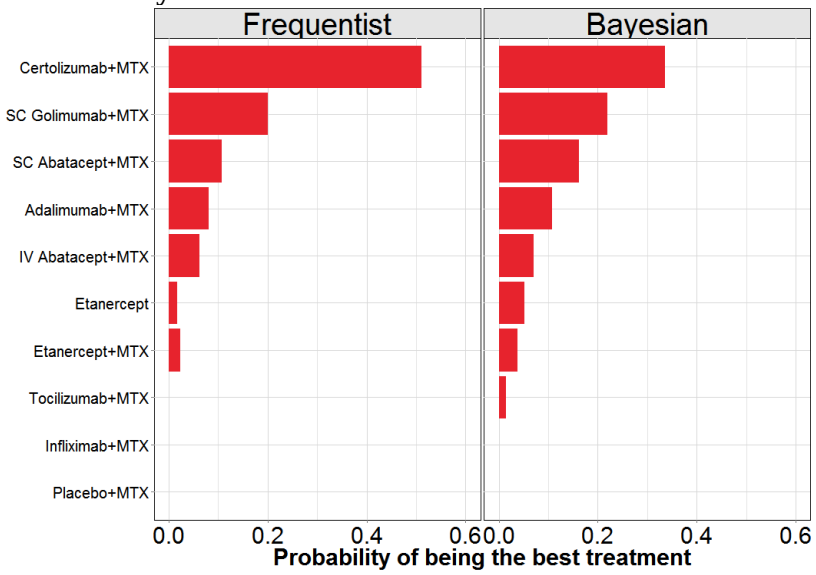


Figure 29: The mean absolute change in HAQ scores as estimated by BMS



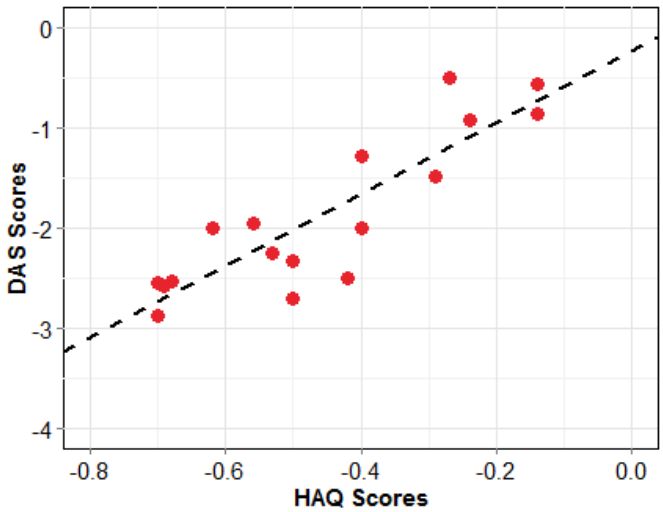
The probability of being the most efficacious treatment is detailed in Figure 30, although the Assessment Group note that, strictly, it is impossible to quantify the probability of being most efficacious using a frequentist approach.

Figure 30: The probability of being the most efficacious treatment (on HAQ score) as estimated by BMS



The analysis of DAS scores by BMS used a linear regression to estimate DAS scores from HAQ scores where these data were not provided. The assumed relationship is shown in Figure 31. No comment was made on the relationship between change in DAS and change in HAQ scores.

Figure 31: The relationship assumed by BMS between HAQ and DAS scores



The network assumed in the DAS analyses therefore replicates that for the HAQ analyses. (Figure 27). As with the HAQ analyses, mean changes in DAS scores, absolute mean changes in DAS scores and the probability of being the most efficacious treatment are provided. These are shown in Figures 32 to 33.

Figure 32: The mean change in DAS scores relative to placebo as estimated by BMS

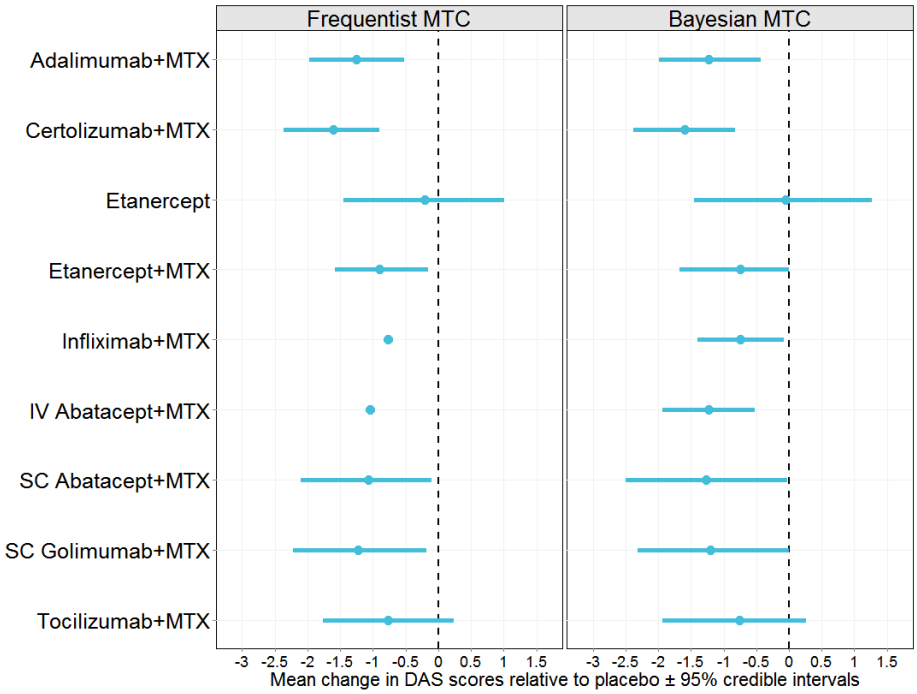
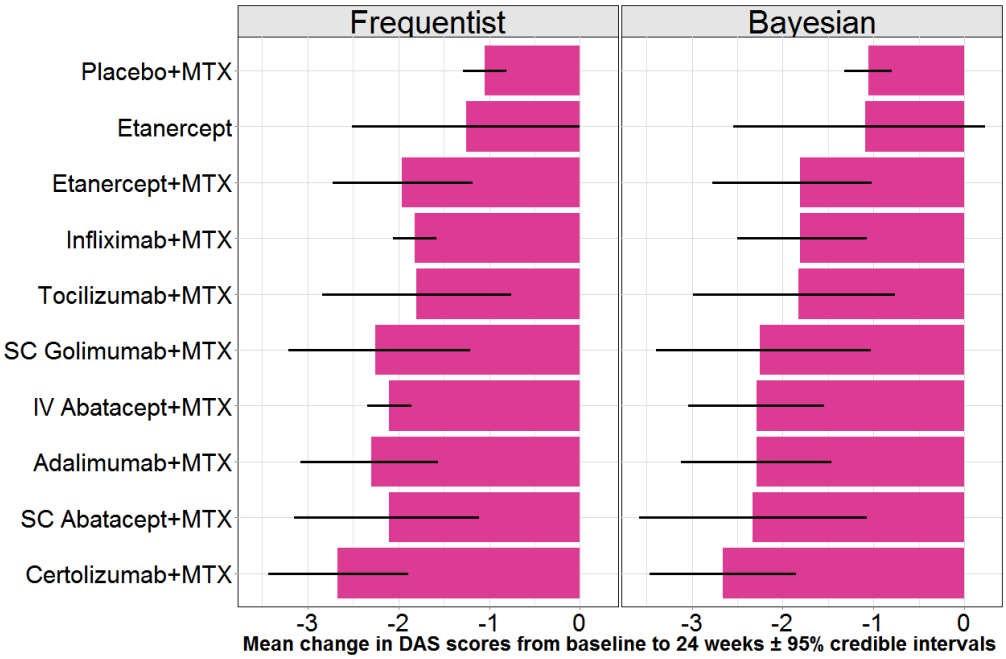
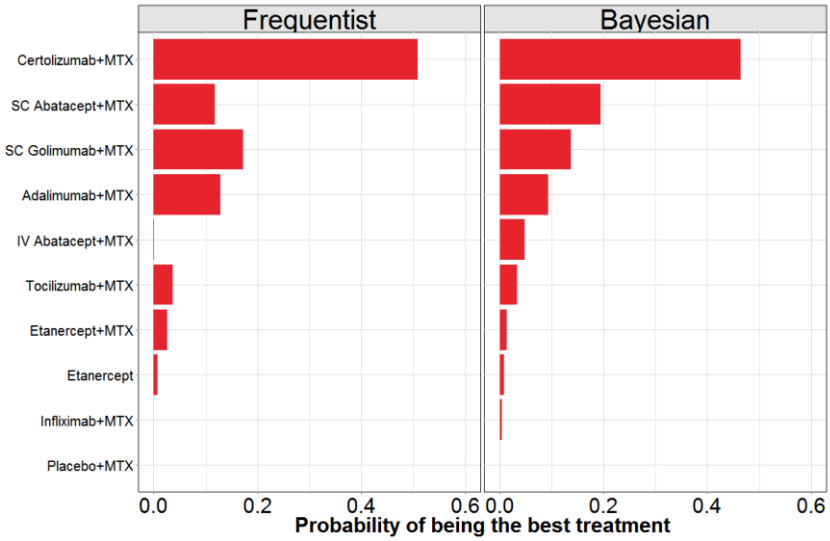


Figure 33: The mean absolute change in DAS scores as estimated by BMS



The probability of being the most efficacious treatment is detailed in Figure 34, although the Assessment Group note that, strictly, it is impossible to quantify the probability of being most efficacious using a frequentist approach.

Figure 34: The probability of being the most efficacious treatment (on DAS score) as estimated by BMS



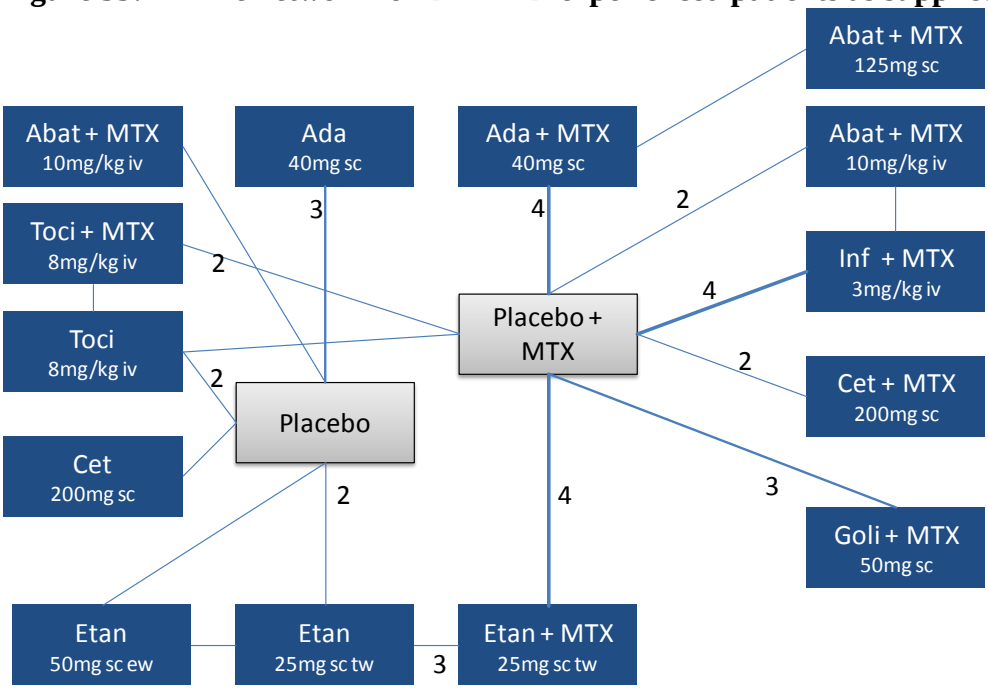
BMS's interpretation of the MTC data

BMS state that "certolizumab + MTX seems to be the best treatment at reducing both HAQ and DAS scores……. golimumab+MTX also appears to be an effective treatment in improving QoL, along with etanercept+MTX and SC abatacept+MTX" and "Infliximab+MTX and etanercept alone are expected to yield the smallest negative changes in both HAQ and DAS scores other than placebo+MTX"

6.2.10.3 MSD

The data used in the MTC conducted by MSD are contained in Tables 16-18 of both the infliximab and the golimumab submission with the network reproduced in Figure 35. No steps were taken to ensure legimitacy (for example, that the ACR 50 value was lower than the ACR20 example).

Figure 35: The network for DMARD-experienced patients as supplied by MSD



MSD present results in terms of the drug that is the focus of the submission (i.e. golimumab or infliximab). The ACR results for golimumab are shown in Figures 36 to 38, whilst those for infliximab are shown in Figures 39 to 41.

Figure 36: ACR20 - DMARD Experienced Patients at 24 Weeks estimated by MSD in the golimumab submission

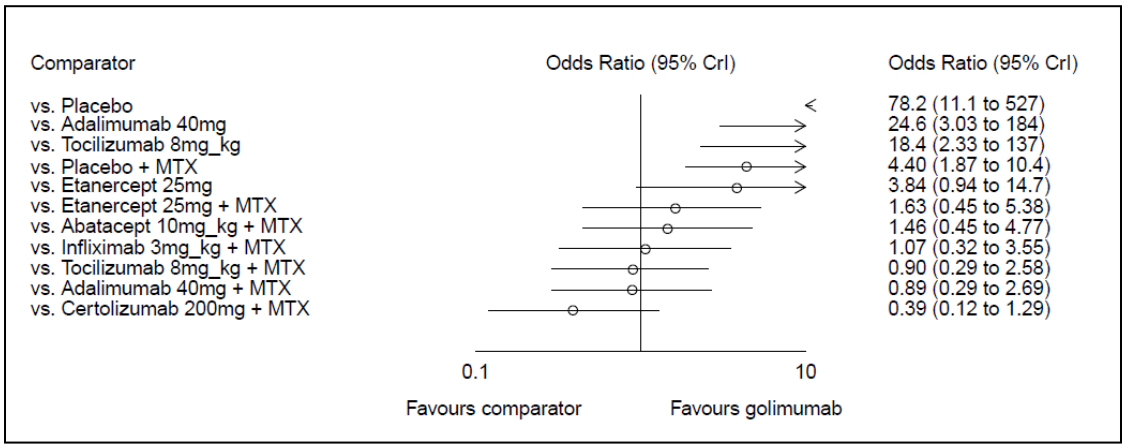


Figure 37: ACR50 - DMARD Experienced Patients at 24 Weeks estimated by MSD in the golimumab submission

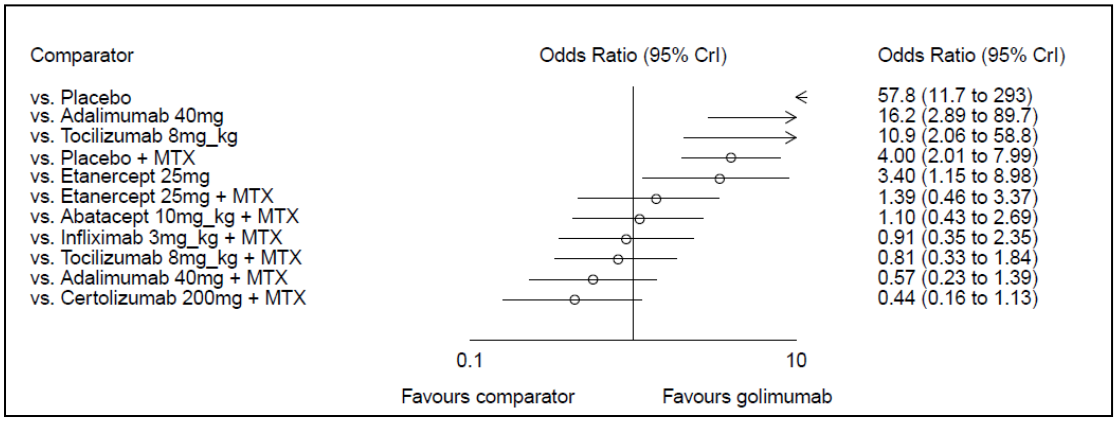


Figure 38: ACR70 - DMARD Experienced Patients at 24 Weeks estimated by MSD in the golimumab submission

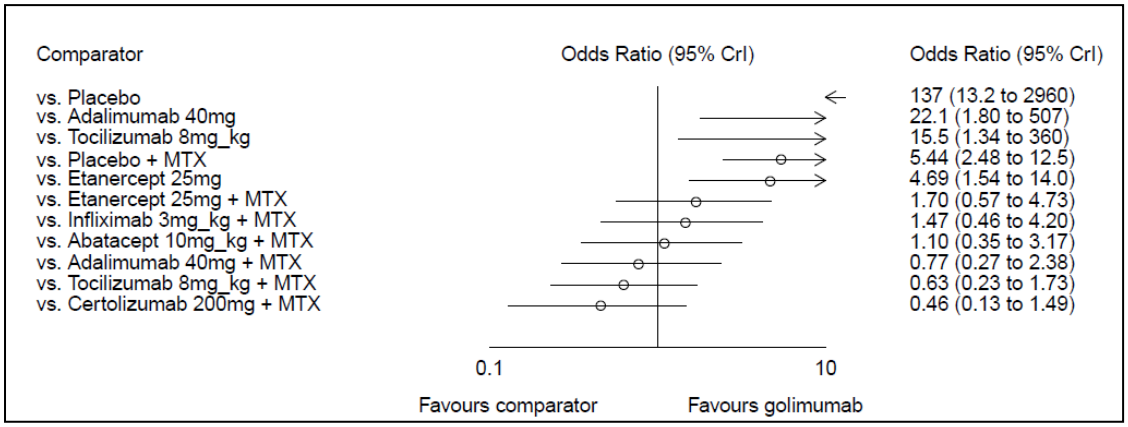


Figure 39: ACR20 - DMARD Experienced Patients at 24 Weeks estimated by MSD in the infliximab submission

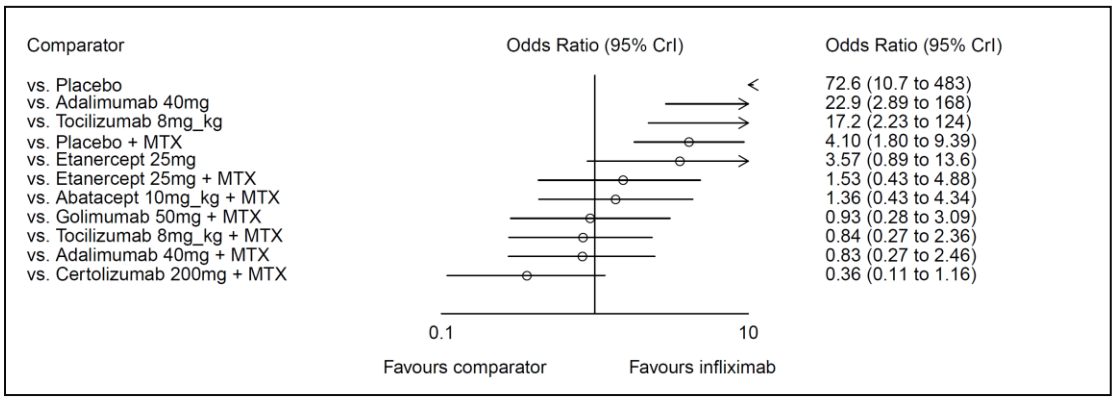


Figure 40: ACR50 - DMARD Experienced Patients at 24 Weeks estimated by MSD in the infliximab submission

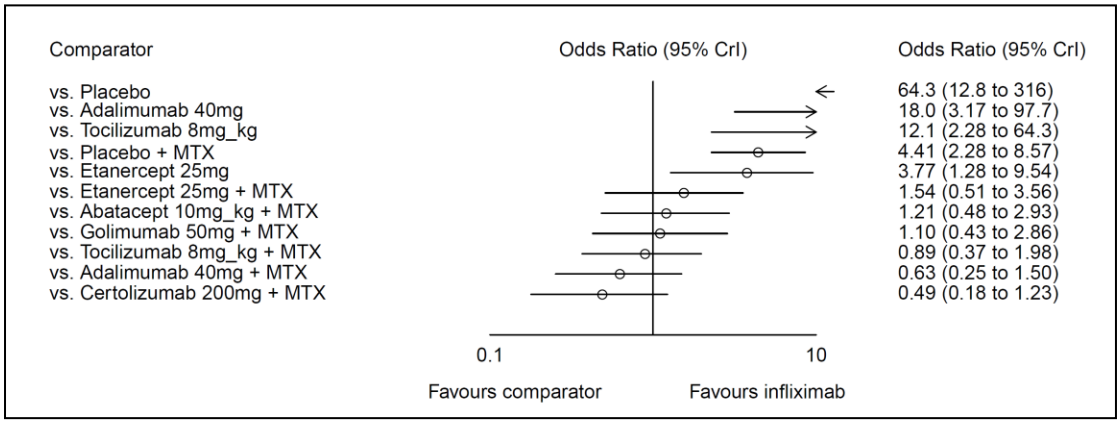
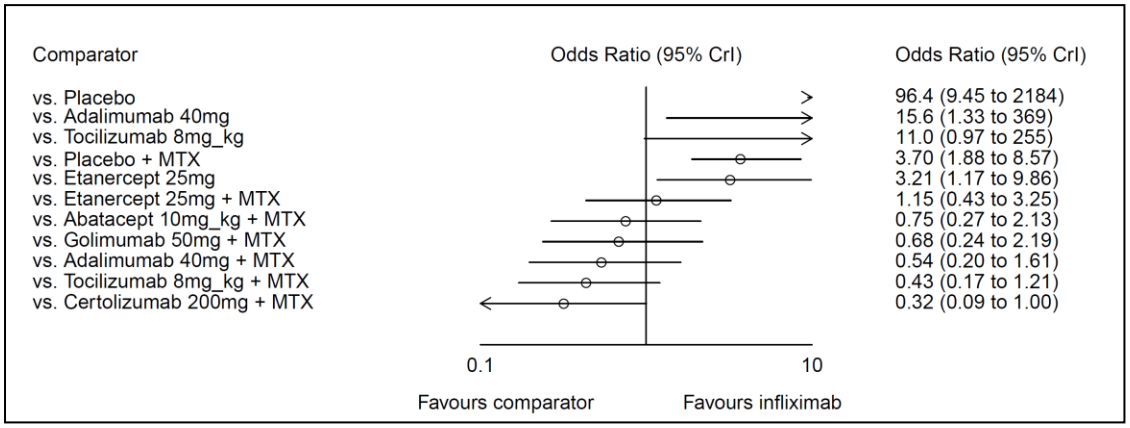


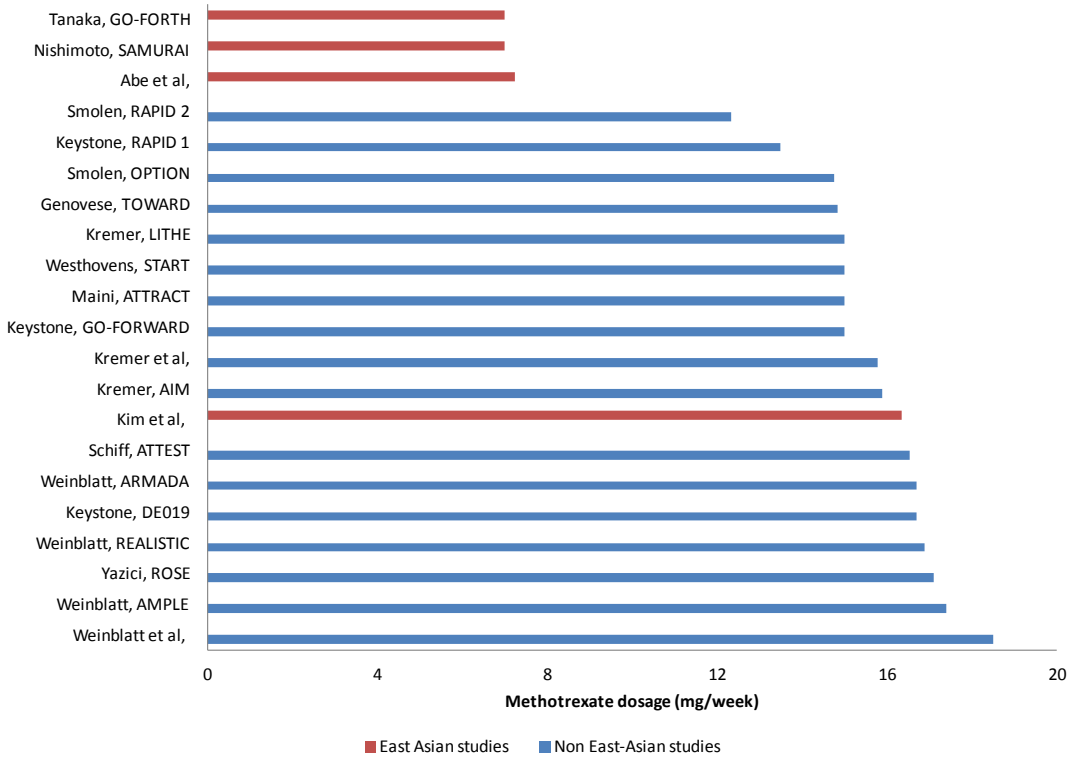
Figure 41: ACR70 - DMARD Experienced Patients at 24 Weeks estimated by MSD in the infliximab submission



MSD conducted sensitivity analyses excluding open-label studies as these may have a higer potential for bias. This did not materially affect the ACR 20 or ACR50 results, but had a larger (although non-patterned) impact at ACR70.

A second sensitivity analyses was conducted where Asian studies were included (Figure 42 reproduces a Figure supplied by MSD and indicates lower background MTX use in these studies).

Figure 42 Comparison of MTX Usage (average mg/week) in East Asian versus Non-East Asian Studies supplied by MSD



The exclusion of non-Asian studies did not markedly alter the odds ratios which remain with wide credible intervals.

MSD's interpretation of the results

MSD summarise the results of the MTC for golimumab and infliximab as below:

o ACR20: no signficant differences were observed between [drug name] and other biologic DMARDs, with the exception of adalimumab monotherapy and tocilizumab monotherapy

o ACR50: no significant differences were observed between [drug name] and other biologic DMARDs, with the exception of adalimumab monotherapy, tocilizumab monotherapy, and etanercept monotherapy

o ACR70: no significant differences were observed between [drug name] and other biologic DMARDs, with the exception of adalimumab monotherapy, tocilizumab monotherapy, and etanercept monotherapy

In each of the exceptions listed above golimumab and infliximab were assumed to be statistically significantly better than the named intervention.

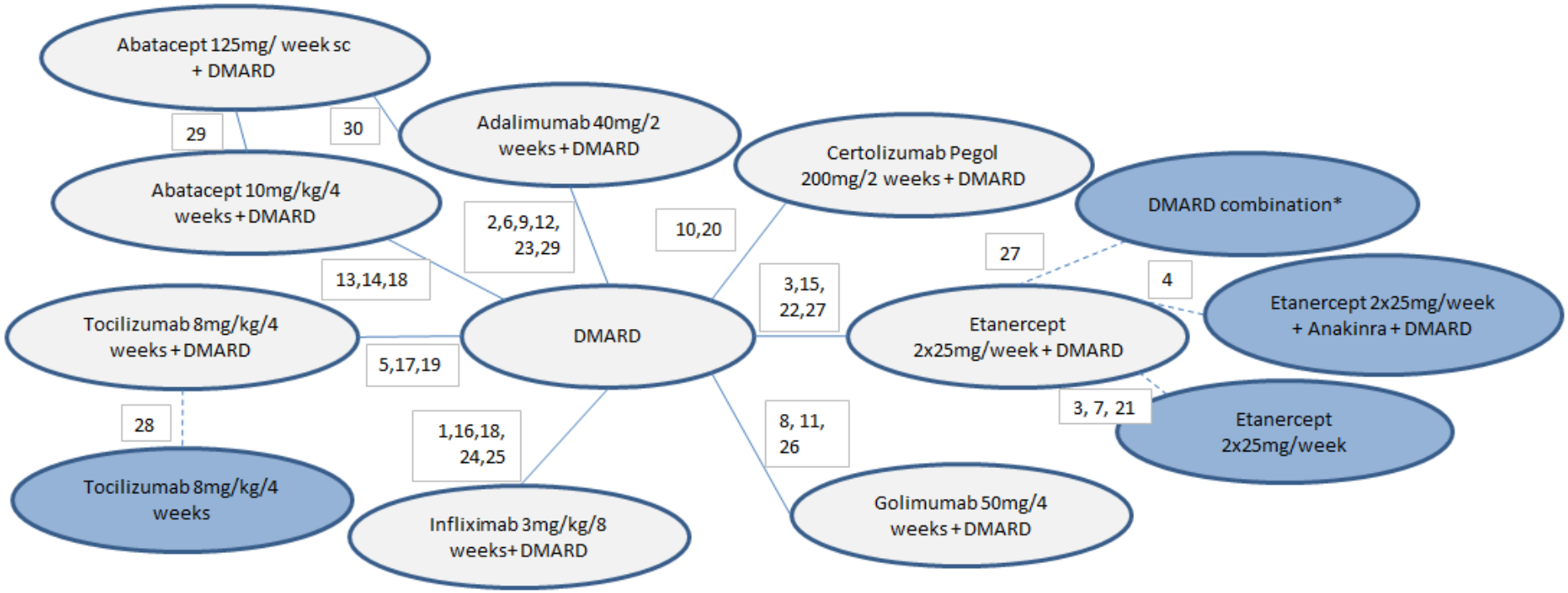
6.2.10.4 Pfizer

Pfizer undertook three separate MTCs: ACR20/50/70 responses for a severe cDMARD-experienced population; HAQ changes for a severe cDMARD-experienced population; and ACR20/50/70 responses for a severe cDMARD experienced population who were treated with bDMARD monotherapy. The networks for these MTCs are reproduced in Figures 43 to 45.

The results produced by each of these analyses in the base case are provided in Tables 119 to 121.

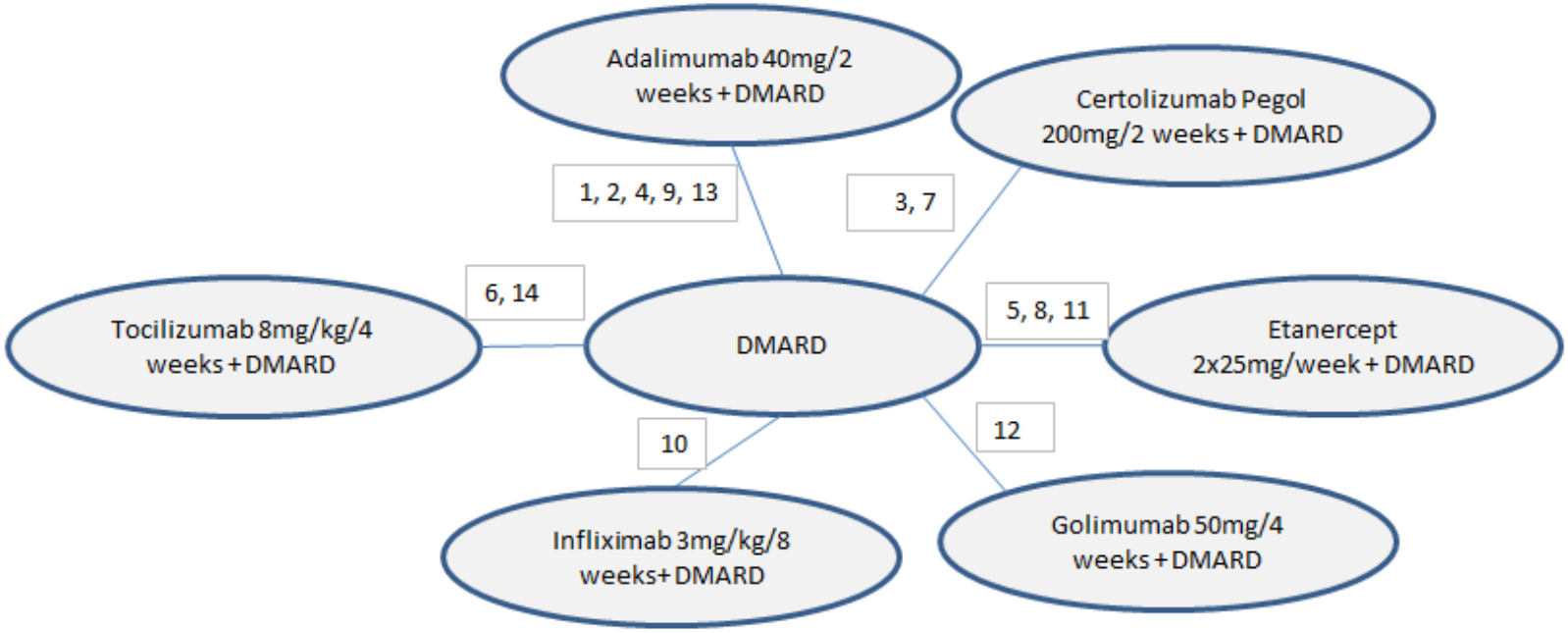
No steps were taken to ensure legimitacy (for example, that the ACR 50 value was lower than the ACR20 example)

Figure 43: The network diagram for combination therapy, ACR responses in severe DMARD experienced patients as produced by Pfizer



Note: numbers refer to key, not to reference list.
Key: 1: Abe 2006; 2: Chen 2009; 3: Combe 2006; 4: Genovese 2004; 5: Genovese 2008 (TOWARD); 6: Huang 2009; 7: Kameda 2010 (JESMR); 8: Kay 2008; 9: Keystone 2004 (DE019); 10: Keystone 2008 (RAPID 1); 11: Keystone 2009 (GO-FORWARD); 12: Kim 2007; 13: Kremer 2003; 14: Kremer 2006 (AIM); 15: Lan 2004; 16: Maini 1999 (ATTRACT); 17: Maini 2006 (CHARISMA); 18: Schiff 2008; (ATTEST); 19: Smolen 2008 (OPTION); 20: Smolen 2009a (RAPID 2); 21: van Riel 2006 (ADORE); 22: Weinblatt 1999; 23: Weinblatt 2003 (ARMADA); 24: Westhovens 2006b (START); 25: Zhang 2006; 26: Tanaka 2012 (GO-FORTH); 27: Kim 2012 (APPEAL); 28: Dougados 2012 (ACT-RAY); 29: Genovese 2011; 30:Weinblatt 2013 (AMPLE)

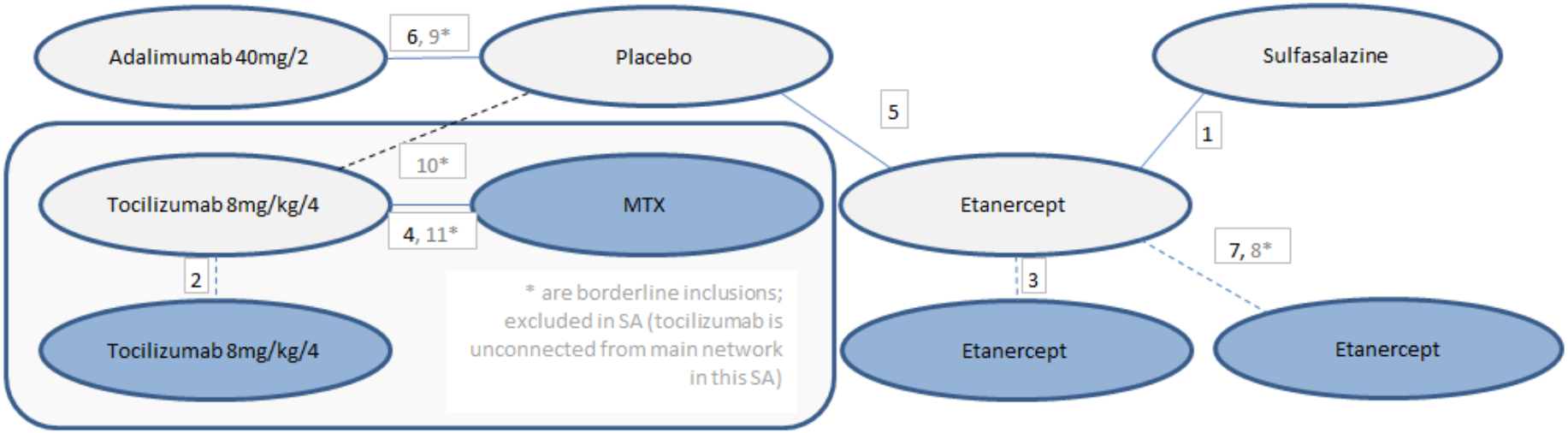
Figure 44: The network diagram for combination therapy, HAQ changes in severe DMARD experienced patients as produced by Pfizer



Note: numbers refer to key, not to reference list.

Key: 1: Chen 2009; 2: Keystone 2004 (DE019); 3: Keystone 2008 (RAPID 1);4: Kim 2007; 5: Lan 2004; 6: Smolen 2008 (OPTION); 7: Smolen 2009a (RAPID 2);8: Weinblatt 1999; 9: Weinblatt 2003 (ARMADA);10: Zhang 2006;11: Combe 2006; 12: Tanaka 2012 (GO-FORTH);13: van Vollenhoven 2012 (ORAL Standard); 14: Genovese 2011

Figure 45: The network diagram for monotherapy, ACR responses in severe DMARD experienced patients as produced by Pfizer



Note: numbers refer to key, not to reference list.

Key: 1: Combe 2006; 2: Dougados 2012 (ACT-RAY); 3: Johnsen 2006; 4: Maini 2006 (CHARISMA); 5: Moreland, 1999; 6: van de Putte 2004; 7: van Riel 2006 (ADORE); 8: Kameda 2010 (JESMR); 9: Miyasaka 2008 (Change); 10: Nishimoto 2004 (STREAM); 11: Nishimoto 2009 (SATORI).

Table 119: The MTC base case results for combination therapy, ACR responses in severe DMARD experienced patients as produced by Pfizer

Treatment	Control	Random effects OR v control (95% CrI)
ACR20		
ETN 2x25mg/week + DMARD	ABA10mg/kg/4 weeks+ DMARD	2.973 (1.288, 7.185)†
ETN 2x25mg/week + DMARD	ABA 125mg/week sc + DMARD	2.970 (1.115, 8.248)†
ETN 2x25mg/week + DMARD	ADA 40mg/2 weeks + DMARD	3.050 (1.366, 7.111)†
ETN 2x25mg/week + DMARD	CZP 200mg/2 weeks + DMARD	0.852 (0.317, 2.338)
ETN 2x25mg/week + DMARD	GOL 50mg/4 weeks + DMARD	2.520 (0.994, 6.711)
ETN 2x25mg/week + DMARD	INF 3mg/kg/8 weeks + DMARD	2.847 (1.250, 6.682)†
ETN 2x25mg/week + DMARD	TOC 8mg/kg/4 weeks + DMARD	2.174 (0.907, 5.477)
ACR50		
ETN 2x25mg/week + DMARD	ABA10mg/kg/4 weeks+ DMARD	3.164 (1.119, 9.683)†
ETN 2x25mg/week + DMARD	ABA 125mg/week sc + DMARD	3.038 (0.920, 10.870)
ETN 2x25mg/week + DMARD	ADA 40mg/2 weeks + DMARD	3.111 (1.139, 9.147)†
ETN 2x25mg/week + DMARD	CZP 200mg/2 weeks + DMARD	1.143 (0.330, 4.087)
ETN 2x25mg/week + DMARD	GOL 50mg/4 weeks + DMARD	2.431 (0.765, 8.130)
ETN 2x25mg/week + DMARD	INF 3mg/kg/8 weeks + DMARD	3.116 (1.115, 9.244)†
ETN 2x25mg/week + DMARD	TOC 8mg/kg/4 weeks + DMARD	2.141 (0.725, 6.950)
ACR70 (continuity corrected [CC])		
ETN 2x25mg/week + DMARD	ABA10mg/kg/4 weeks+ DMARD	5.321 (1.103, 46.550)†
ETN 2x25mg/week + DMARD	ABA 125mg/week sc + DMARD	5.228 (0.968, 49.190)
ETN 2x25mg/week + DMARD	ADA 40mg/2 weeks + DMARD	4.956 (1.052, 43.980)†
ETN 2x25mg/week + DMARD	CZP 200mg/2 weeks + DMARD	1.646 (0.258, 16.337)
ETN 2x25mg/week + DMARD	GOL 50mg/4 weeks + DMARD	3.702 (0.632, 34.352)
ETN 2x25mg/week + DMARD	INF 3mg/kg/8 weeks + DMARD	5.445 (1.150, 48.140)†
ETN 2x25mg/week + DMARD	TOC 8mg/kg/4 weeks + DMARD	2.654 (0.529, 23.680)

Abbreviations: ABA, Abatacept; ADA, Adalimumab; CC data with continuity correction; CrI, credible interval (Bayesian probability interval); CZP, certolizumab pegol; DMARD, disease-modifying anti-rheumatic drugs (MTX or SUL); ETN, etanercept; exp, experienced; GOL, golimumab; INF, infliximab; MTX, MTX; OR, odds ratio; SUL, sulfasalazine, TOC, Tocilizumab. Note: medians are presented as the best estimate for the central value, since means may be overly influenced by outliers; † Licensed ETN combination has significantly higher odds of ACR outcome compared with other licensed bDMARD combination (based on the 95% CrI).

Table 120: The base case MTC results for combination therapy, HAQ changes in severe DMARD experienced patients, etarnercept vs other bDMARDs as produced by Pfizer

Treatment	Control	WMD v control (95% CrI)
ACR20		
ETN 2x25mg/week + DMARD	ADA 40mg/2 weeks + DMARD	-0.051 (-0.236, 0.127)
ETN 2x25mg/week + DMARD	Certolizumab pegol 200mg/2 weeks + DMARD	0.032 (-0.164, 0.218,)
ETN 2x25mg/week + DMARD	GOL 50mg/4 weeks + DMARD	-0.053 (-0.299,0.181)
ETN 2x25mg/week + DMARD	INF 3mg/kg/8 weeks + DMARD	-0.044 (-0.317,0.219)
ETN 2x25mg/week + DMARD	TOC 8mg/kg/4 weeks + DMARD	-0.101 (-0.308,0.100)

Abbreviations: CrI, credible interval (Bayesian probability interval); DMARD, disease-modifying anti-rheumatic drugs; ETN, etanercept; TOC, Tocilizumab; WMD , weighted mean difference.

Table 121: The MTC base case results for monotherapy, ACR responses in severe DMARD experienced patients as produced by Pfizer

Treatment	Control	Random effects OR v control (95% CrI)
ACR20		
ETN 2x25mg/week	ADA 40mg/2 weeks	2.797 (0.104, 70.572)
ETN 2x25mg/week	TOC 8mg/kg/4 weeks	0.384 (0.008, 17.430)
ETN 2x25mg/week	SUL	7.485 (0.526, 106.508)
ACR50		
ETN 2x25mg/week	ADA 40mg/2 weeks	3.300 (0.186, 57.078)
ETN 2x25mg/week	TOC 8mg/kg/4 weeks	0.252 (0.003, 10.440)
ETN 2x25mg/week	SUL	5.685 (0.591, 56.370)
ACR70 (continuity corrected data)		
ETN 2x25mg/week	ADA 40mg/2 weeks	1.935 (0.051, 131.285)
ETN 2x25mg/week	TOC 8mg/kg/4 weeks	0.436 (0.000, 73.390)
ETN 2x25mg/week	SUL	19.936 (1.159, 908.265)†

Abbreviations: ADA, Adalimumab; CrI, credible interval (Bayesian probability interval); DMARD, disease-modifying anti-rheumatic drugs; ETN, etanercept; exp, experienced; SUL, sulfasalazine, TOC, Tocilizumab. Note: medians are presented as the best estimate for the central value, since means may be overly influenced by outliers; † Licensed ETN has significantly higher odds of ACR outcome compared to other licensed DMARD (based on the 95% CrI).

Pfizer's interpretation of the MTC results

Pfizer state that for combination therapy in cDMARD experienced severe RA patients "ETN was consistently significantly better than ABT IV, ADA and INF for ACR20/50/70 outcomes. Furthermore, with regards to ACR20/70 outcomes ETN was shown to be significantly better than ABT (sc), otherwise was similar in efficacy to CZP, GOL, and TOC."

For combination therapy in cDMARD experienced severe RA patients Pfizer state that "though all bDMARDs had significantly lower HAQ compared to DMARD control at follow-up, none of the bDMARDs had significantly lower HAQ compared with each other.

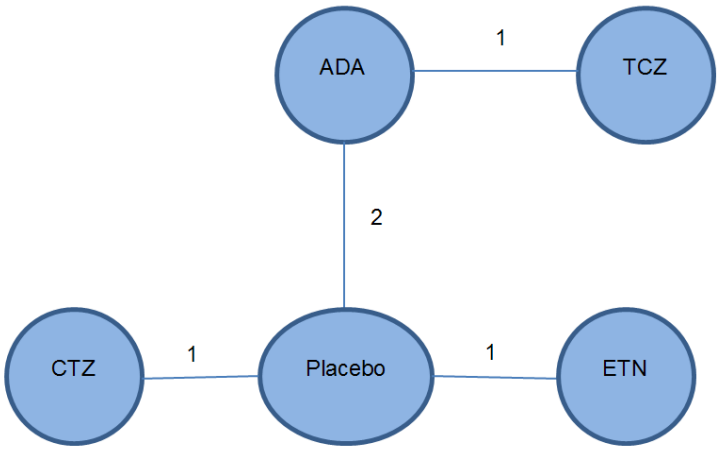
For cDMARD experienced severe RA patients who are treated with monotherapy Pfizer state that "based on the random-effects network meta-analysis; adalimumab, etanercept and tocilizumab have significantly higher odds of ACR 70 than placebo and etanercept and tocilizumab have significantly higher odds of ACR 50 than placebo but none of the bDMARDs are significantly better than another"

The conclusion made by Pfizer in the executive summary is that " the network meta analysis in this submission demonstrated that etanercept is significantly better than adalimumab and infliximab for ACR20/50/70 outcomes. Furthermore, etanercept was shown to be significantly better than abatacept iv with regards to ACR20/50/70 outcomes and abatacept subcutaneous for ACR20/70."

6.2.10.5 Roche

Roche report that "the proportion of patients who fall within each response category was informed by a network meta-analysis, performed within a Bayesian framework. This meta-analysis was undertaken to allow indirect comparison of tocilizumab monotherapy with biologics currently recommended by NICE for use as monotherapy in the DMARD-IR setting." Figure 46 reproduces the model setup supplied by Roche. The number of trials informing each 'link' in the meta-analysis is indicated next to each line.

Figure 46: The network of studies included in the meta-analysis undertaken by Roche



CTZ, certolizumab pegol; ADA, adalimumab; ETN, etanercept; TCZ, tocilizumab

The ACR outcomes adjusted within the framework of the network meta-analysis used within the economic model by Roche are presented in Table 122.[207] Unadjusted ACR rates are provided for

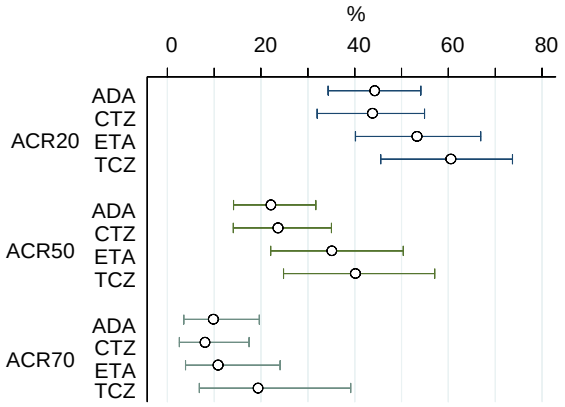
comparison. The forest plot in Figure 47 was produced by Roche and gives an overview of the uncertainty about each estimate after adjustment in the meta-analysis.[114,193,208]

Figure 47: Results from the meta-analysis conducted by Roche

Table 122: ACR response by treatment – unadjusted and adjusted

Treatment	ACR20	ACR50	ACR70
Adjusted Values (from network meta-analysis):	%	%	%
ADA	44	22	10
CTZ	44	24	8
ETA	53	35	11
TCZ	61	40	19
Unadjusted Values:	%	%	%
ADA	49	28	18
CTZ	44	23	7
ETA	59	40	15
TCZ	65	47	33

Figure 1: Biologic monotherapy ACR responses used in economic model



Graphic shows adjusted percentage responses from network meta-analysis with 95% confidence intervals.

Roche's interpretation of the MTC results

Roche state that "results from the analysis suggest that tocilizumab monotherapy was associated with superior outcomes on ACR20, ACR50 and ACR70 response measures, compared with adalimumab, certolizumab pegol and etanercept monotherapy."

6.2.10.6 UCB

UCB undertook mixed treatment comparisons at both 12 and 24 weeks for each ACR response, and also DAS28 (ESR) remission and low disease activity (24 week data only). These analyses were undertaken for both bDMARDs in combination with MTX and bDMARD monotherapy (with the exception of DAS28 (ESR) low disease activity). The results have, however, been marked as academic-in-confidence.

The results for combination therapy are shown in Figures 48 to 51. The results for monotherapy are shown in Figures 52 to 55

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[redacted]

[redacted]

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[redacted]

UCB's interpretation of the results from the MTC.

In the circumstance where a patient can receive MTX UCB state that "The MTC conducted showed that certolizumab pegol plus MTX is at least as effective to the other comparators considered in the vast majority of cases. The RR of that certolizumab pegol plus MTX vs. comparators in combination with MTX was greater than one for all outcomes investigated for the majority of cases, which indicated better outcomes in favour of that certolizumab pegol plus MTX. The wide credible intervals noted in most of these cases reflect the minimal differences in relative clinical effect between certolizumab pegol and the comparators considered."

In the circumstance where bDMARD monotherapy is used UCB state that "The MTC showed that certolizumab pegol was at least as effective to the other monotherapies considered. In the majority of cases, the RR of certolizumab pegol compared to the other monotherapies considered was greater than one, however, no differences were statistically significant.

6.2.11 Responder Criteria

This section details the criteria to be designated a responder within the submissions. In summary, five submissions used ACR response as a measure of a responder. Three of these assumed that ACR 20 measured at 24 weeks / 6 months was the minimal response, one (AbbVie) assumed that an ACR 50 response was required, with one (UCB) allowing an evaluation of ACR20 at either 3 or 6 months. The UCB submission used a EULAR response of moderate or good (at either 3 or 6 months) in those with moderate to severe disease. The BMS submission assumed a DAS 28 reduction of 1.2 at 6 months to designate a responder.

6.2.11.1AbbVie

The minimal response required for continuation of treatment after the initial 6 month period is ACR50. The Assessment Group note that the comparative results for AbbVie's intervention (adalimumab) appears to perform relatively better using ACR50 than by using ACR20

6.2.11.2BMS

Inadequate treatment is determined by the change in DAS28 – in the base case defined as DAS28 score not improved by at least 1.2 by month 6. Patients who discontinue within the first 6 months would then try another first-line biologic.

6.2.11.3MSD

Response is defined as at least an ACR20 response at 24 weeks.

6.2.11.4Pfizer

Patients were assumed to discontinue therapy if response (defined as at least an ACR20 response) was not achieved citing previous NICE submissions.[204,209,210]

6.2.11.5Roche

Response is defined as at least an ACR20 response at 24 weeks.

6.2.11.6UCB

The responder definition in the submission from UCB is variable due to the flexibility of the model. For the severe disease activity population a response of at least ACR20 is required to continue treatment. For the moderate disease activity population at least a moderate EULAR response was required. The time at which response was measured could be varied between 3 and 6 months.

6.2.12 HAQ / EQ-5D changes in relation to response levels

This section details how the submissions related response levels to changes in HAQ. In summary, the majority of submissions assessed the associated HAQ change with response levels from their own data and then assumed that this was applicable to all bDMARDs. All submissions showed that a greater response was associated with a greater HAQ reduction. UCB used EQ-5D data recorded within their trials to model the improvement post response. There was not a consistent approach to modelling how the response was assumed to be accumulated. This ranged from assuming that the response at six months was assumed to be experienced throughout the six month response perios, that it was accumulated linearly, or that the full effect was applied but a one-off reduction modelled to assume that the HAQ improvement would not be observed immediately.

6.2.12.1AbbVie

AbbVie assumed that the HAQ change by ACR response for all bDMARDs would be the same as for adalimumab, while the changes associated with conventional DMARDs would be the same as for MTX.

HAQ changes are divided into the initial response period (defined as either 12 or 24 weeks) and then from the response period until 52 weeks. The base case assumes a 24 week response period.

HAQ changes are assumed to be linear until the response period and linearly between the response period and week 52.

Inputs for the MTX-naive patients were based on the DE013 trial (AbbVie, data on file) and those for MTX-experienced patients were from the DE019 trial (AbbVie, data on file). AbbVie report that data specific for monotherapy were not available in DE019 trial thus an assumption was made that the relative HAQ changes for monotherapy in MTX-experienced patients were similar to those observed in the MTX-naive patients (i.e., DE013). As sample sizes were deemed insufficient for analysis of relative changes in HAQ by stage or RA (moderate or severe), data were pooled for moderate and severe patients.

Tables 123 to 125 reproduce the data supplied by AbbVie.

Table 123: The relative change reported by AbbVie in HAQ score by ACR response by treatment - moderate and severe RA, MTX-experienced for bDMARD plus MTX

	ADA + MTX			MTX		
	mean % change	**SD**	**N**	**mean % change**	**SD**	**N**
Baseline to 24 weeks						
ACR <20	-13.7%	72.5%	41	-5.6%	57.6%	88
ACR20-<50	-38.6%	33.0%	52	-31.5%	33.6%	41
ACR50-<70	-55.7%	30.1%	42	-55.5%	30.3%	14
ACR70-100	-80.0%	22.5%	38	-74.0%	31.7%	6
24-52 weeks						
ACR <20	4.7%	45.4%	32	-3.2%	44.2%	74
ACR20-<50	-2.1%	73.5%	41	5.5%	45.7%	34
ACR50-<70	-12.8%	51.7%	33	2.8%	32.1%	11
ACR70-100	-40.0%	48.6%	17	-22.9%	14.7%	2

Source: DE019 pooled data for moderate (3.2 < DAS28 ≤ 5.1) and severe (DAS28 > 5.1) disease activity

Table 124: The relative change reported by AbbVie in HAQ score by ACR response by treatment - severe RA, MTX-naive for bDMARD plus MTX

	ADA + MTX			MTX		
	Mean % Change	**SD**	**N**	**Mean % Change**	**SD**	**N**
Baseline to 24 weeks						
ACR <20	-30.4%	43.0%	36	-27.9%	36.2%	48
ACR20-<50	-53.1%	38.5%	41	-43.3%	45.2%	53
ACR50-<70	-61.8%	31.9%	51	-53.7%	44.2%	52
ACR70-100	-83.6%	24.0%	108	-82.9%	22.7%	62
24–52 weeks						
ACR <20	-25.2%	28.5%	26	10.7%	104.2%	35
ACR20-<50	-12.1%	40.9%	24	-4.6%	58.2%	42
ACR50-<70	-28.8%	62.5%	34	-11.4%	47.9%	43
ACR70-100	-14.5%	80.2%	50	-24.6%	60.3%	28

ACR = American College of Rheumatology; ADA = adalimumab; MTX = MTX; SD = standard deviation
Source: DE013 (PREMIER) pooled data for moderate and severe [AbbVie data on file]

Table 125: The relative change reported by AbbVie in HAQ score by ACR response by treatment - moderate and severe RA, MTX-experienced or naïve for bDMARD monotherapy

	ADA			MTX		
	Mean % Change	**SD**	**N**	**Mean % Change**	**SD**	**N**
Baseline to 24 weeks						
ACR <20	-18.7%	43.6%	70	-27.9%	36.2%	48
ACR20-<50	-45.8%	33.8%	50	-43.3%	45.2%	53
ACR50-<70	-68.0%	26.8%	48	-53.7%	44.2%	52
ACR70-100	-83.2%	23.7%	52	-82.9%	22.7%	62
24–52 weeks						
ACR <20	-10.1%	41.9%	50	10.7%	104.2%	35
ACR20-<50	22.2%	112.3%	38	-4.6%	58.2%	42
ACR50-<70	31.1%	135.8%	35	-11.4%	47.9%	43
ACR70-100	54.0%	199.7%	22	-24.6%	60.3%	28

ACR = American College of Rheumatology; ADA = adalimumab; MTX = MTX; SD = standard deviation
Source: DE013 [AbbVie data on file] pooled data for moderate and severe

6.2.12.2BMS

BMS provides a Table that details the assumed reduction in HAQ. This is reproduced in Table 126. The Assessment Group comment that it has been assumethat the HAQ reduction for cDMARDs used after bDMARDs was halved, however the data for bDMARDs used after an initial bDMARD appear to generally perform better than the same bDMARD used first line.

BMS report that since the improvement in HAQ-DI score upon starting each treatment would actually be more gradual than a sudden decrease, “start and end effects” are applied as a one-off deduction in quality-adjusted life years (QALYs) upon starting and ending each treatment. This deduction is equal to 20% of the increase in quality of life. No justification for this value was provided.

Table 126: The assumed reduction in HAQ detailed by BMS

Treatment	HAQ (reduction) change from baseline - mean	HAQ change from baseline – standard error	Source
1st line biologics			
IV abatacept	0.344	0.063	BMS MTC (2013)
SC abatacept	0.332	0.112	
Adalimumab	0.326	0.077	
Etanercept	0.279	0.097	
Infliximab	0.199	0.063	
Tocilizumab	0.213	0.100	
Golimumab	0.333	0.112	
Certolizumab pegol	0.386	0.069	
2nd line biologics			
IV abatacept	0.5	0.05	Malottki et al (2011)[186]
Adalimumab	0.48	0.048	Malottki et al (2011)[186]
Etanercept	0.35	0.035	Malottki et al (2011)[186]
Infliximab	0.35	0.035	Malottki et al (2011)[186]
Tocilizumab	0.39	0.039	Strand et al (2012)[211]
Golimumab	0.25	0.025	Smolen et al (2009)[212]
Rituximab	0.4	0.04	Malottki et al (2011)[186]
DMARDs			
Leflunomide	0.24	0.024	Chen et al (2006)[113] - halved
Injectable gold	0.2	0.02	Chen et al (2006)[113] - halved
Cyclosporin A	0.2	0.02	Chen et al (2006)[113] - halved
Azathioprine	0.1	0.01	Chen et al (2006)[113] - halved

Table 33: HAQ-DI change from baseline

For 2nd line biologics and DMARDs, the standard deviation is assumed to be 10% of the mean. DMARDs: disease modifying anti-rheumatic drugs; HAQ-DI: Health Assessment Questionnaire Disease Index; IV: intravenous; SC: subcutaneous. Malottki et al (2011) assumed halved the change in HAQ-DI from Chen et al (2006) as this was for an earlier line indication.

6.2.12.3MSD

MSD present EQ-5D data for patients dependent on their health state (non-responder, ACR20; ACR50; ACR50). These values have been calculated with the HAQ score being transformed to a utility using the equation of Hurst et al.[213] 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. MSD does not comment on this discrepancy.

a) Golimumab data

Table 127 provides data on the assumed utility for each health state. These data have been taken from Go-Forward[191] and Go-Forth[214] for the DMARD experienced population and from Go-Forward for the severe subgroup. These values have been calculated by the HAQ score being used within the Hurst mapping.

Table 127: Utility assumed by health state by MSD in the golimumab submission

Health state	DMARD experienced	DMARD experienced severe subgroup (DAS>5.1) (GO-FORWARD)
Baseline	0.401	0.355
GOL treated non-responder	0.461	0.362
GOL treated ACR 20	0.581	0.636
GOL treated ACR 50	0.638	0.689
GOL treated ACR 70	0.787	0.790

b) Infliximab data

Table 128 provides data on the assumed utility for each health state. These data have been taken from START[108] and ATTRACT[67] for the DMARD experienced population and from ATTRACT for the severe subgroup. These values have been calculated by the HAQ score being used within the Hurst mapping.

Table 128: Utility assumed by health state by MSD in the infliximab submission

Health state	DMARD experienced	DMARD experienced severe subgroup (DAS28 >5.1) (ATTRACT)
Baseline	0.282	0.271
IFX treated non-responder	0.307	0.290
IFX treated ACR20	0.462	0.452
IFX treated ACR50	0.568	0.554
IFX treated ACR70	0.684	0.660

6.2.12.4Pfizer

Pfizer present the HAQ improvement associated with each of four response levels: No ACR response; ACR 20; ACR 50; and ACR70. Pfizer state that following a systematic review only one reference allowed separate estimates to be made for c-DMARD-IR and bDMARD-IR.[204]

This source permitted the estimation of HAQ change associated with each ACR response category separately for both cDMARD-IR (first line within a treatment sequence) and bDMARD-IR (second and subsequent lines within a treatment sequence) patients. Table 129 presents the estimates of HAQ improvement used in cDMARD-IR and bDMARD-IR patients. Pfizer note that this approach may lead to further uncertainty in the model due to the extra mapping function, so a comparison using available HAQ data from the NMA was undertaken as a sensitivity analysis.

Table 129: The HAQ improvement by ACR response category reported by Pfizer

ACR response	cDMARD-IR		bDMARD-IR	
	Mean	**SE**	**Mean**	**SE**
No response	0.136	0.017	0.098	0.022
ACR 20	0.443	0.018	0.405	0.034
ACR 50	0.668	0.026	0.670	0.058
ACR 70	0.923	0.032	0.949	0.064

Abbreviations: ACR, American College of Rheumatology; bDMARD-IR, biological disease modifying antirheumatic drug inadequate responder; DMARD-IR, DMARD-inadequate response; SE, standard error.

6.2.12.5Roche

The Roche analysis assumes that response to treatment has an impact on disease severity (as measured by individual HAQ score). Data from ADACTA[208] was analysed to estimate the relationship between ACR response and individual HAQ score for the first 24 weeks. The data from the first 24 weeks of the study suggest that the higher the observed ACR response the greater the drop in HAQ score. Table 130 presents the individual HAQ score drop per ACR response and the corresponding standard errors.

For every response to a new treatment, the model applies the corresponding HAQ score reduction to every simulated individual during the first cycle on treatment (first six months). The relationship between ACR response and initial HAQ drop is assumed to be conditional only to ACR response; it is applied universally to all interventions.

Table 130: Improvement in HAQ score associated with ACR response assumed by Roche

ACR response	Mean	SE	Source
No response	0.11	0.00797	ADACTA
ACR20	0.44	0.00709	
ACR50	0.76	0.01433	
ACR70	1.07	0.00832	

6.2.12.6UCB

UCB recorded EQ-5D data within the RAPID trials which was used for patients with severe RA and within the CERTAIN study for those will moderate to severe RA. These are detailed in Table 131 although the data for CERTAIN was marked academic-in-confidence.

The data for the severe population was calculated using a regression analysis of EQ-5D vs. ACR in RAPID trials, no further information was provided.

The data for the severe population was calculated using a regression analysis of [redacted]

Table 131: The EQ-5D data reported by UCB associated with response level

Severe RA population		Moderate to severe RA population	
No response	0.062	[redacted]	[redacted]
ACR20	0.173		
ACR50	0.238		
ACR70	0.358		

6.2.13 HAQ trajectory following initial response

This section details the HAQ trajectory post the initial response. In summary, the majority of submissions use data from previous NICE appraisals although the Assessment Group comment that the evidence base for these values is very limited. Given that HAQ progression is linked in the majority of models to utility, disease costs, and mortality any inaccuracies in the projected HAQ trajectories could have a marked impact on the results.

6.2.13.1AbbVie

AbbVie report that In line with current NICE guidance on the use of adalimumab, etanercept and infliximab for the treatment of RA[215], the model assumes different levels of HAQ progression for patients receiving anti-TNF therapy, conventional DMARD therapy and non-responders after one year. The assumption on long-term HAQ-DI progression while on biological therapy is based on the results of a variety of long-term studies on adalimumab and etanercept.[100,216,217]

Table 132: Absolute annual HAQ-DI progression

	HAQ-DI progression
Biologic therapy	0.000 [a]
Conventional DMARD	0.045 [b]
Non-responders	0.060 [b]

Two sensitivity analyses were undertaken changing: the HAQ-progression whilst on bDMARDs to 0.030; and the HAQ-progression on cDMARDs to 0.030

6.2.13.2BMS

BMS assume that the HAQ score increases (clinically worsens) gradually over time while the patient is receiving treatment with DMARDs or palliative care. This is modelled as an increase of 0.125 every 2.7 years on DMARDs and 0.125 every 2 years on palliative care. It is assumed that patients on bDMARDs have a constant HAQ. These assumptions are based on Malottki et al.[186]

6.2.13.3MSD

In the MSD model the HAQ score declines at a rate of 0.045 per year if a patient is receiving cDMARDs. Patients receiving palliative care have an assumed HAQ progression of 0.06 per year. The model assumes that biologic DMARD treatment halts disease progression, that is a HAQ progression of 0.00 per year. This assumption is aligned with comments from the NICE technology appraisal TA130 which states that it is "appropriate to primarily examine the estimates of cost-effectiveness based on the assumption of no HAQ progression while on TNF- α inhibitor therapy, while acknowledging the effects on the estimates of incorporating different assumptions of HAQ progression" and assumes the same holds true for the other biologic DMARDs.

6.2.13.4Pfizer

Pfizer assume an annual HAQ progression rate of 0.00 for bDMARDs, 0.046 for cDMARDs and 0.06 per year for palliative care citing that these values have been used in previous NICE appraisals.

Different rates of HAQ progression were explored as sensitivity analyses in both Moderate to Severe and Severe Naïve populations.

Scenario analysis within the Moderate to Severe population uses rates of progression observed within PRESERVE Period 2 week 36–88 Rates of progression in Period 2 of PRESERVE were greater for MTX than those used in previous economic evaluations. While rates of HAQ for ETN+MTX initially increase in the first four weeks after randomisation, but these stabilise from week 40 to week 88 suggesting little or no further HAQ progression over this period. HAQ change from week 36, 40, and 56 to wk 88 for both ETN+ MTX and MTX alone has been included in the sensitivity analyses.

Scenario analysis within the Severe Naïve population uses rates of progression from Period 2 of COMET week 52-104. [redacted]

A further scenario analysis within the all populations uses rates of progression (0.031 for cDMARDs and 0.0102 for bDMARDs) observed by Scott et al, 2000.[218]

6.2.13.5 Roche

Roche report that there is a dearth of evidence on the changes a patient's condition undergoes whilst on treatment. Moreover, there are no available data from the Roche clinical trials [ACT-RAY and ADACTA[208,219]] following the first 24 weeks (first cycle).

For these reasons Roche states that their model uses evidence in previous submissions to NICE. The model assumes no HAQ score progression for all treatments while patients continue responding. For patients in palliative care, a per-cycle HAQ score progression (worsening) of 0.03 is assumed.

Table 133: HAQ progression while on treatment per cycle after the initial 24 week period

Treatment	HAQ score change per 6-month cycle	Source
All biologics	0.00	NICE TA 130
Palliative care	0.03	NICE TA 130

6.2.13.6 UCB

In the UCB model it was assumed that HAQ would decrease at a rate of 0.1913 per annum whilst on treatment, but increase by 0.048 per annum when a second line bDMARD was used. However it appears that there are typographical errors within the model as the 6 month response on bDMARDs was half that of the 3 month response, and the changes at 3 months and 6 months for follow up biologics were equal. For patients on palliative care or cDMARDs HAQ progression was assumed to be 0.06 per annum. UCB cite previous NICE guidance for these figures except the HAQ change on first line treatment that was calculated from data on file.

6.2.14 Time to discontinuation of treatment

This section details the methods used by the manufacturers to determine when a patient discontinued treatment. In summary a multitude of methods were used by the manufacturers.

6.2.14.1AbbVie

Time to treatment discontinuation curves from Edwards et al. (2005[220]) (based on GPRD data) were used to model overall (due to any reasons) withdrawal c DMARDs. AbbVie state that these curves, although somewhat dated, have been judged as representative of withdrawal patterns from non-biologic DMARDs today by a practicing UK rheumatologist; although it was indicated that withdrawal due to hydroxychloroquine was not expected to be so low. Assumptions were made for combination DMARDs not examined by Edwards et al that time on treatment would be similar to time on treatment with MTX.

The digitised curves (reading in 90+ points from each curve) were used to create mock patient level data—following the method of Hoyle & Henley[221] when number of patients at risk was available (anti-TNFs) and Tierney et al.,[222] when number of patients at risk is unavailable (DMARDs). Parametric survival models were estimated using SAS (and STATA for Gompertz), and provided parameter estimates and variance-covariance matrices. For the time to treatment discontinuation data the exponential, Weibull, Gompertz, lognormal, loglogistic and gamma survival models were

estimated. The gamma model was only estimated for information purposes, as the Arena model submitted by AbbVie cannot generate samples from it. The fits of the curves were compared visually, as well as using the Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Curves for MTX, SSZ and HCQ in the GPRD study were fitted best by the lognormal function and these were, therefore, used for modelling time on treatment. The fitted curves to the data are shown in Table 134. The correlation between the parameters was not provided in the report.

Table 134: The estimated lognormal curve for cDMARD withdrawal rate calculated by AbbVie

Treatment	Lambda		Gamma	
	Mean	SE	Mean	SE
MTX	2.1163	0.0531	2.8986	0.0472
MTX+HCQ[a]	2.1163	0.0531	2.8986	0.0472
SSZ+HCQ[a]	2.1163	0.0531	2.8986	0.0472
LEF[a]	2.1163	0.0531	2.8986	0.0472
HCQ	0.4165	0.0802	2.1706	0.0674
SSZ	0.6336	0.0303	2.4548	0.0259
CYC[b]	0.6336	0.0303	2.4548	0.0259

CYC = ciclosporin; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = MTX; SE = standard error;
SSZ = sulfasalazine

a. Assume similar time on treatment as MTX

b. Assume similar time on treatment as sulfasalazine

AbbVie state that "for anti-TNFs, separate withdrawal curves by reason either through adverse or lack of efficacy are presented in the published literature. Modelling these two reasons separately allows more flexibility in modelling the time on treatment and corresponds to the new treat to target paradigm; for patients on non-biologic DMARDs, they would be evaluated monthly and could start dropping off immediately, while for those on biologics, patients would have to stay on the drug for at least three to six months for the assessment of response.[223]"

Patients on biologics are subjected to risk of withdrawal due to AEs immediately after start of therapy based on analysis of BSRBR data presented in Soliman et al.[224] The same withdrawal pattern was assumed applicable for all biologic therapies including anti-TNFs due to lack of data on the newer biologics not included in BSRBR, the lack of recent comparative data across anti-TNFs in BSRBR,

and conflicting comparative withdrawal evidence about the anti-TNFs in the international literature.[225,226] Biologic monotherapy was assumed to have a higher withdrawal rate due to AEs (evidenced by a recent BSRBR based analysis, Soliman et al., 2011[224]).

AbbVie comment that although the Cochrane review found evidence of differences among clinical trials of biologics, various design elements (e.g., mandatory and optional early escape in some but not all trials) make it difficult to compare withdrawal and to generalise trial results for long-term withdrawal patterns.

The Gompertz model fitted best in the AbbVie analyses for the AE-specific withdrawal data from BSRBR for all anti-TNFs presented by Soliman et al, 2011.[224] It assumes that after approximately 9 years on biologic treatment, there would be no further withdrawals due specifically to AEs (i.e., all long-term withdrawals are due to lack of efficacy). This was consistent with the experience of a UK practicing clinician consulted by AbbVie. AbbVie stated that since the Gompertz survival model is a proportional hazard model, published reason-specific adjusted hazard ratios in the same study for the anti-TNF monotherapy versus anti-TNF combination therapy with MTX have been applied to obtain monotherapy withdrawal curves.[224] The paper did not present reason-specific Kaplan-Meier curves for anti-TNFs as monotherapy vs anti-TNF+MTX specifically. The assumption used was that overall anti-TNF AE withdrawal curve is identical to the combination therapy AE withdrawal curve. This assumption is supported by data from the study in which similar proportions of patients discontinued the treatment due to adverse events at year 5, this was shown between those receiving anti-TNFs in combination with MTX and the overall anti-TNF cohort (28% vs. 29%, see Table 2 in Soliman et al. In addition, the Kaplan-Meier curves of the observed overall persistence between these two groups run very close to each other (Table 134). Parameter estimates for modelling of withdrawals due to AEs for biologics are shown in Soliman et al.

Figure 56: Kaplan–Meier estimates of the observed persistence with all anti-TNFs and with the combination therapy of anti-TNFs and MTX in BSRBR

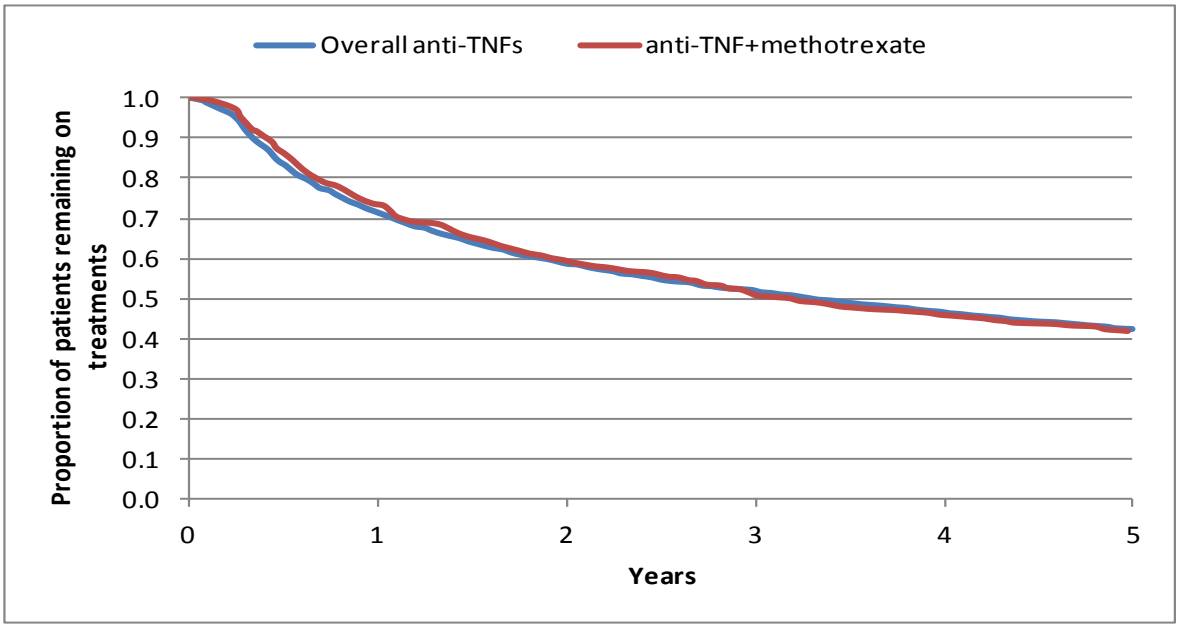


Table 135 provides data on withdrawals from bDMARD therapy due to adverse events. The correlation between the parameters was not provided in the report.

Table 135: Parameter estimates for biologic treatment withdrawal due to AEs (Gompertz Function) calculated by AbbVie

Treatment	Lambda		Gamma	
	Mean	SE	Mean	SE
Combination with MTX	-1.5164	0.0308	-0.6247	-0.0005
Monotherapy	-1.1311[a]	0.0308	-0.6247	-0.0005

SE = standard error

a. Estimated by applying the published adjusted hazard ratio of 1.47 to the lambda parameter of the combination therapy[24]

Data on withdrawal due to LoE have been presented for overall anti-TNF groups by the same study.[224] This curve starts sloping downwards at around three months, and the slope is very flat i.e., there is no evidence of a stopping rule being applied despite clinical guidance on stopping patients on biologic therapy if adequate response is not observed at six months.[223]

In the AbbVie base case, the model applies a stopping rule based on response rates; all those without an ACR 50 or ACR 20 (in a sensitivity analysis) response would be stopped at a given time (i.e., 12 or

24 weeks). AbbVie state "therefore, the initial part of the withdrawal curve due to lack of efficacy from BSRBR is ignored. The differences in response rates would result in differential withdrawal due to lack of efficacy on biologics, including monotherapy versus combination therapy (i.e., with MTX); no additional adjustment would be applied. Beyond the time point of response assessment, the lack of efficacy curves from BSRBR would be applied to allow for further drop out due to lack of efficacy. In other words, the model predicts a time to withdrawal due to lack of efficacy for all patients in the simulation when each treatment is initiated. If the time predicted is earlier than the stopping rule (i.e., 12 or 24 weeks), it is ignored. If it is later than the stopping rule, and the patient is a responder not stopping treatment at e.g., 12 or 24 weeks, they would be withdrawn at that time".

For withdrawal beyond the non-responder withdrawal (i.e., at 12 or 24 weeks), the same curve is applied across all biologics.

Due to the flat initial part of the withdrawal due to LoE curve, AbbVie report that no survival model provided a good fit to the overall data. However, the fit was much improved when the flat part of the curve for the initial 3.337 months was removed from the data. The best fit for the truncated data was provided by the lognormal function. Time to withdrawal due to lack of efficacy predicted from these parameters was added back by 3.337 months in the simulation. Table 136 provides the parameter estimates given by AbbVie. The correlation between the parameters was not provided in the report.

Table 136: Parameter estimates for biologics treatment withdrawal due to LoE (LogNormal Function) provided by AbbVie

Treatment	Lambda		Gamma	
	Mean	SE	Mean	SE
Biologics	3.1171	0.0643	3.0225	0.0512

SE = standard error

6.2.14.2BMS

The probabilities of adverse events assumed by BMS are shown in Table 28. The source for these data appears to be a mixed treatment comparison (MTC) of adverse events undertaken within the BMS submission. As with the MTC for comparative efficacy the reporting of the MTC assumptions is lacking.

Table 137: The probability of adverse event for first-line biologics assumed by BMS

	At Month 6/Week 24
Treatment	**Probability of adverse event**
IV abatacept	0.023
SC abatacept	0.016
Adalimumab	0.041
Etanercept	0.030
Infliximab	0.086
Tocilizumab	0.041
Golimumab	0.020
Certolizumab pegol	0.096

IV: intravenous; SC subcutaneous.

For all first-line biologic treatments, if an adverse event had not been simulated then time on treatment is sampled from a Weibull distribution with shape parameter 0.71 and scale parameter 7.06, giving a mean time on treatment 4.21 years (BMS's submission document to NICE for TA234).

BMS assumes that the probability of having an adverse event on rituximab is 3.54%, as 17 of 480 patients discontinued due to adverse events in the REFLEX study.[227] If the patient does not discontinue treatment with rituximab at 6 months, their long-term time on rituximab is sampled from a Weibull distribution with shape 0.474 and scale 5.1.[202]

Malottki et al.,[202] considered IV abatacept, adalimumab, etanercept, infliximab and rituximab, so BMS state that it was necessary to find inputs for SC abatacept, golimumab and tocilizumab. SC abatacept was assumed to have the same efficacy and safety profile as IV abatacept. The early withdrawal inputs for golimumab and tocilizumab came from the GO-AFTER study[228] and the RADIATE study,[229] respectively. Golimumab is an anti-TNF, so the long-term time on treatment is assumed to be the same as that of the other anti-TNFs -(adalimumab, etanercept and infliximab) as reported by Malottki et al. Tocilizumab is not an anti-TNF, but, in the absence of data, the long-term time on treatment is assumed to be the same as that of the anti-TNFs. Inputs for short-term and long-term time on treatment are shown in Table 138 and Table 139, respectively.

Table 138: The probability of early discontinuation on second-line biologics as estimated by BMS

Treatment	Parameter	Point estimate (%)
Adalimumab	Probability of withdrawal at 12 weeks	9.9
	Proportion of the discontinuations at 12 weeks that are due to ineffectiveness	56.2
Etanercept	Probability of withdrawal at 13 weeks	5.2
	Proportion of the discontinuations at 13 weeks that are due to ineffectiveness	16.7
Infliximab	Probability of withdrawal at 16 weeks	23
	Proportion of the discontinuations at 16 weeks that are due to ineffectiveness	66.7
Abatacept	Probability of withdrawal at 24 weeks	13.6
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	25.7
Tocilizumab	Probability of withdrawal at 24 weeks	14.7
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	64.5
Golimumab	Probability of withdrawal at 24 weeks	12.4
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	72.0

Third-line tocilizumab use was assumed to have the same rate of adverse events, and time to withdrawal as second-line tocilizumab treatment.

Table 139: The long-term time on second-line biologics as estimated by BMS

Treatment	Alpha	Beta	Mean (years)
Adalimumab	0.701	3.21	4.06
Etanercept	0.701	3.21	4.06
Infliximab	0.701	3.21	4.06
Abatacept	0.81	5.49	6.17
Tocilizumab	0.701	3.21	4.06
Golimumab	0.701	3.21	4.06

For cDMARDs, BMS used data reported by Malottki et al. These data are reproduced in Tables 140 and 141.

Table 140: The probability of early discontinuation cDMARDs as assumed by BMS

Treatment	Parameter	Point estimate (%)
Leflunomide	Probability of withdrawal at 6 weeks	13
	Probability of withdrawal at 6-24 weeks	30
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	33.2
Injectable gold	Probability of withdrawal at 6 weeks	14
	Probability of withdrawal at 6-24 weeks	27.1
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	66.7
Cyclosporin A	Probability of withdrawal at 6 weeks	8
	Probability of withdrawal at 6-24 weeks	24
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	50
Azathioprine	Probability of withdrawal at 6 weeks	15
	Probability of withdrawal at 6-24 weeks	25
	Proportion of the discontinuations at 24 weeks that are due to ineffectiveness	50

Table 141: Long-term time on cDMARDs as assumed by BMS

Treatment	Alpha	Beta	Mean (years)
Leflunomide	1	5.98	5.98
Injectable gold	0.48	1.81	3.91
Cyclosporin A	0.5	4.35	8.70
Azathioprine	0.39	4.35	15.53

6.2.14.3MSD

MSD state that no studies with sufficient follow-up were identified for golimumab, adalimumab, certolizumab, tocilizumab or abatacept. The long-term drop-out rates for golimumab were assumed equivalent to those for infliximab treated patients. This is a very conservative assumption given that the drop-out rate after 52 weeks of golimumab 50 mg is very low in the GO-FORWARD clinical trial,[191] only 6% at week 52. The long-term drop-out rates for the other biologic DMARDs from clinical trials are more aligned with the evidence available for infliximab. Keystone[230] report comparable drop-out rates at week 52 to those observed in a 52 week trial for infliximab.

A summary of the probability of discontinuation due to long-term loss of efficacy parameters used by MSD is shown in Table 142.

Table 142: Time to treatment withdrawal assumed by MSD

Long-term discontinuation due to loss of efficacy				
Treatment	**Lambda (λ)**	**Gamma (γ)**	**Mean (years)**	**Source**
Golimumab	0.103	0.532	9 years	Assumed equal to infliximab
Adalimumab	0.103	0.532	9 years	Assumed equal to infliximab
Infliximab	0.103	0.532	9 years	
Etanercept	0.027	0.738	12 years	
Certolizumab	0.103	0.532	9 years	Assumed equal to infliximab
Tocilizumab	0.103	0.532	9 years	Assumed equal to infliximab
Abatacept IV	0.103	0.532	9 years	Assumed equal to infliximab
Abatacept SC	0.103	0.532	9 years	Assumed equal to infliximab
MTX	0.091	0.438	20 years	

6.2.14.4 Pfizer

Pfizer used five-year data from the etanercept cohort of the BSRBR to estimate treatment cessation. This was selected because it represented the most appropriate long-term evidence available. Calculations in the etanercept cohort were made separately for combination and monotherapy patients. Severe disease status (relative to Moderate to Severe disease status) was included within the analysis as a covariate, allowing separate estimates of treatment cessation for both Severe and Moderate to Severe populations.

Whilst Pfizer acknowledge the limitations of the use of the ETN BSRBR cohort in the Moderate to Severe population, in the absence of any long-term data in this population these estimates were considered the best available. It is hypothesised that such patients may be at greater risk of progression than a more representative Moderate to Severe population, and therefore treatment cessation may be overestimated within this cohort. In the absence of data in the Severe DMARD-naïve patient population, treatment discontinuation was assumed to be equivalent to that of the Severe DMARD-IR combination therapy population.

Parametric survival curves were fitted to the data with the log-logistic distribution found to provide the best fit to data based on the Akaike Information Criterion.[231] Figure 57 presents the estimated cumulative hazard of treatment cessation vs the observed treatment cessation for the etanercept BSRBR cohort, both combination and monotherapy, although these are marked as commercial-in-confidence.

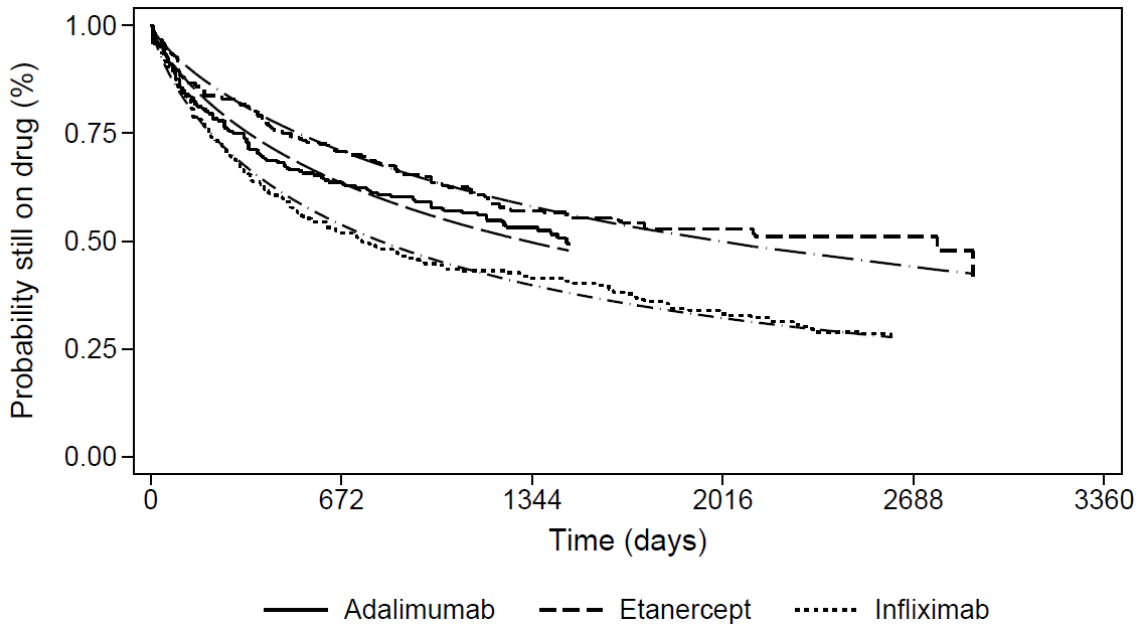
[redacted]

[redacted]

Data for treatment discontinuation were not accessible for comparator therapies from the BSRBR. Therefore, an observational study by Hetland et al.,[232] was selected which presented Kaplan-Meier curves for all-cause treatment cessation for etanercept, infliximab and adalimumab from the DANBIO registry[233] which was considered the most similar to the UK population from registries identified in a Pfizer systematic review. Curves were digitised using Enguage Digitizer[234] and a pseudo-patient-level dataset was created for all three therapies.[221,235,236] These datasets were used to fit log-logistic parametric survival models which provided relative treatment effects for both infliximab and adalimumab vs etanercept. (Figure 58)

These relative effects were applied to the baseline estimates for etarnercept from the BSRBR in order to generate time-on-treatment estimates for infliximab and adalimumab.

Figure 58: The Fitted log-logistic survival distributions estimated by Pfizer



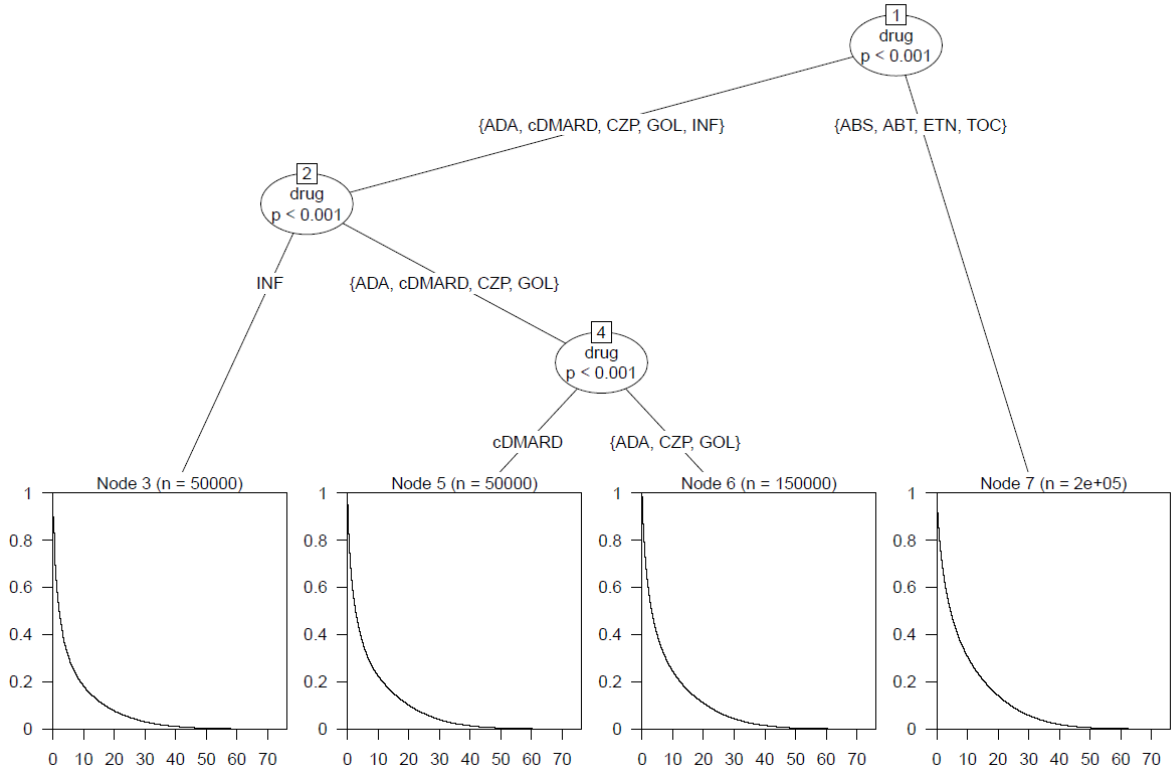
In the absence of long-term data for other therapies, the relative effect for ADA was assumed by Pfizer to apply to certolizumab pegol and golimumab, on the basis that they are also monoclonal antibodies (mAbs). Tocilizimumab, abatacept iv, abatacept sc and rituximab were conservatively assumed to share the same time on treatment as etanercept. A scenario analysis was performed by Pfizer in which there was assumed to be no difference in treatment cessation between bDMARDs.

A cDMARD curve was also generated from the BSRBR control cohort, and this was used for all cDMARDs. Severe disease status (relative to Moderate to Severe disease status) was also included within the analysis as a covariate. Figure 59 (commercial-in confidence) presents the time on treatment assumptions graphically for the Severe DMARD-IR combination therapy population. [redacted]

[redacted]

As Pfizer believe it st is difficult to appreciate differences in treatment cessation across all therapies within Figure 59 the same data is presented as a conditional inference tree in Figure 60. A conditional inference tree performs univariate partitioning of the simulated times to treatment cessation by using a significance test procedure in order to identify differences between time on treatment by therapy. Differences in treatment cessation are identified where partitioning occurs. There are four resulting patterns of 'times' based on the assumptions described previously; infliximab, cDMARD, those based on that of adalimumab (certolizumab pegol and golimumab) and those based on that of etanercept (abatacept iv, abatacept sc, tocilizumab and rituximab).

Figure 60: Conditional inference tree of 1st line treatment cessation, showing patterns of treatment cessation within the economic model, (left to right) shortest to longest times presented by Pfizer



The resulting treatment cessation curves for the model 1st line therapy were adjusted by Pfizer to reflect the increased risk of cessation in subsequent lines of therapy. The (log) time ratio for 2nd line vs 1st line therapy was estimated as -0.365 using the same methodology of patient-level dataset generation as described above, with data taken from DANBIO.[233] This effect was applied in all subsequent lines of therapy and to all therapies (including cDMARDs). Figure 60 presents a comparison of original data and model output. Note that the model output here does not include the effects of the treatment discontinuation rule. The model by default actually models time to start of next therapy (rather than end of current therapy); in order to provide a representative comparison, the time between cessation of rituximabtherapy and the start of the next therapy was ignored in the generation of Figure 61 The model was able to recreate the effects of 2nd and subsequent line treatment cessation accurately.

Figure 61: Treatment cessation in second and subsequent lines estimated by Pfizer

A

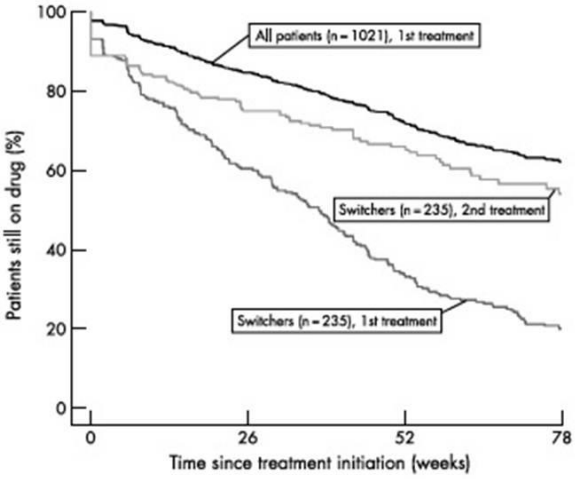
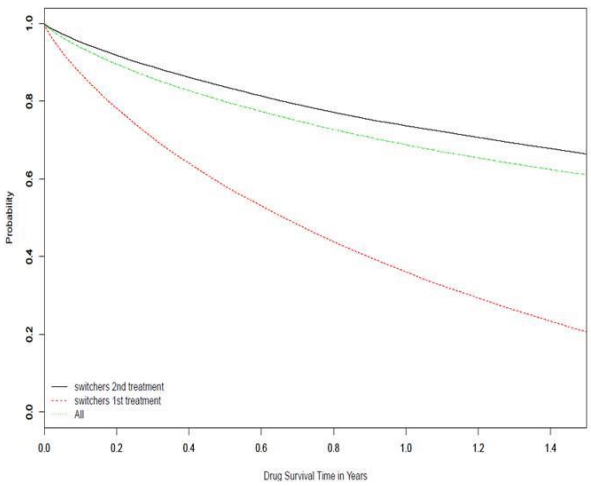


Figure 1 Drug survival during the first and second treatment of all switchers (n = 235) and in the whole population (all rheumatoid arthritis patients receiving their first biological therapy, n = 1021). Kaplan–Meier plots are shown.

B



Treatment cessation data used in the model is presented in Table 143. Times were generated stochastically for each patient using a random number combined with the inverse survival distributions.[152]

Table 143: Log-logistic survival models for all-cause treatment cessation as estimated by Pfizer

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative treatment effects from log-logistic survival model (vs. ETN) †				
Parameter	**Coefficient**			
ADA vs. ETN	-0.412‡			
IFX vs. ETN	-0.905			
Relative treatment effects from log-logistic survival model (vs. ETN)				
Parameter	**Coefficient**			
Subsequent lines vs. 1st line use	-0.365			

Abbreviations: SE, standard error; † Unless specified, the relative treatment effect was assumed to be 0.000. ‡ Also used for certolizumab pegol and golimumab.

6.2.14.5 Roche

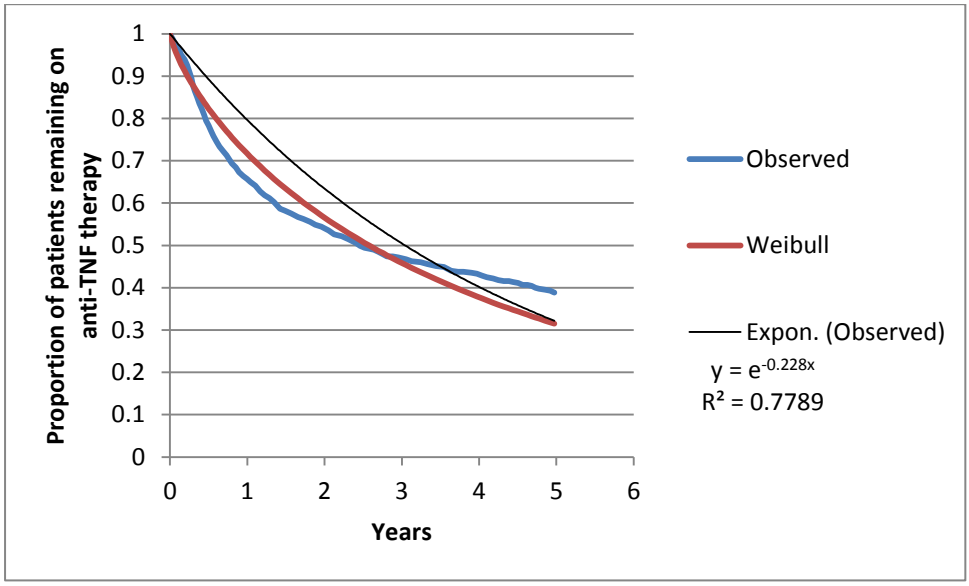
The Roche model assumes that all patients receive each treatment for a minimum of one cycle, until response is evaluated. This is consistent both with previous evidence submissions and with the available efficacy evidence. At 6 months patients will continue on their first therapy, providing they achieved a response greater than or equal to ACR20. Therapy is stopped for a non-responding patient, and they move on to the next drug.

Soliman and colleagues published an analysis of treatment duration using British Society for Rheumatology Biologics Register (BSRBR) data (large cohort with N=10,396[224]). A proportion of these patients do not receive any concomitant DMARD treatment (32.1% N=3,339) and this fact was

used in the economic analysis as a basis for estimating the withdrawal risk of patients receiving biologic monotherapy.

Roche provided a Kaplan-Meier curve showing treatment persistence with anti-TNF. A Weibull and an exponential model were explored to derive a discontinuation rate from the Kaplan-Meier curve. Both models appear to overestimate discontinuation. Roche assumed that the steep rate of discontinuation in the first 2 years reflects the "non-responders", whereas the flat rate after 2.5 years reflects the "good-responders". Roche fitted an exponential distribution to the Kaplan-Meier curve after the first 2.5 years and used that as the probability of discontinuation from treatment for patients with initial response; annual rate of 0.098 (R^2=0.99), 6-month probability of 0.05.

Figure 62: The Weibull and exponential model fitted by Roche to data from Soliman et al. 2011



An adjustment to these curves is based on data from Anderson et al.,[237] a study that explores predicting factors of response to treatment in rheumatoid arthritis. The study suggests that disease duration is one of the most important factors predicting response. Anderson analysed data from randomised control trials of drugs or devices in RA, and found that the disease duration effect on odds of response was 0.98 per extra year of disease duration. This is not included in the base case but has been tested in the sensitivity analysis.

6.2.14.6UCB

UCB present data on the risk of treatment discontinuation due to adverse events explicitly and due to all causes. The discontinuation due to adverse events was denoted academic-in-confidence.

[redacted]

For all discontinuations the time spent on treatment was based on values from a study including over 2,300 patients treated with a TNF-α inhibitor over nine years (DuPan et al. 2009[226]). Results from this study showed that the median time on treatment with a TNF-α inhibitor was 37 months (3.08 years). The same treatment duration was assumed for all biologics.

6.2.15 Rebound post treatment

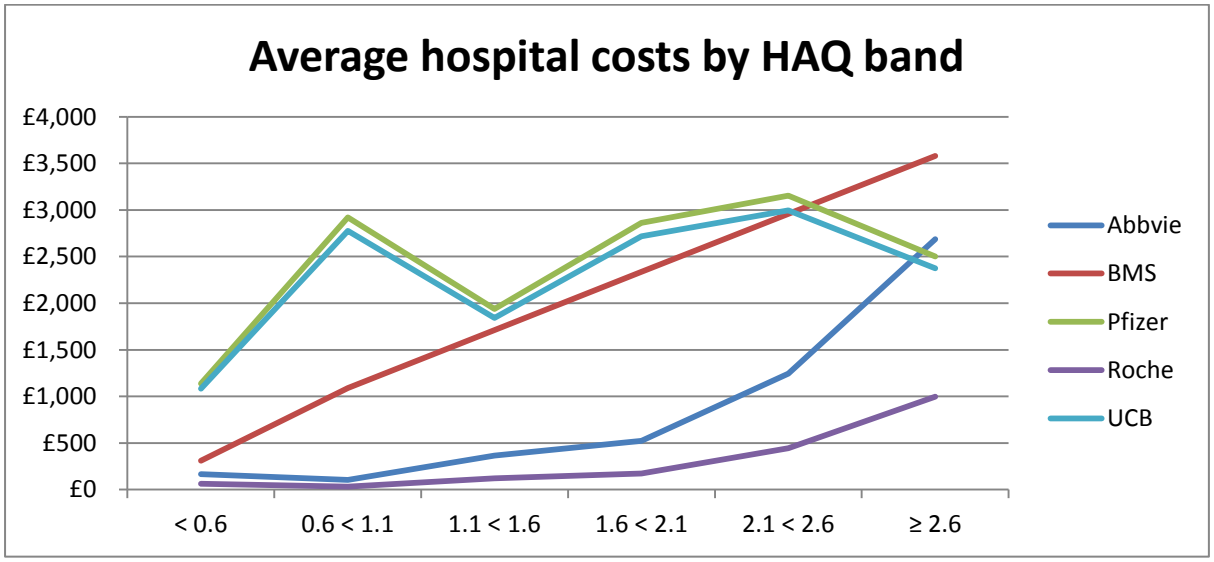
All Interventions

Following the cessation of treatment a patient's HAQ score is updated to reflect the loss of HAQ improvement on the previous line of therapy. MSD, Pfizer, Roche and UCB conduct sensitivity analyses around this assumption. UCB assume that the loss of efficacy from the previous treatment and the gain in efficacy from the subsequent treatment happen simultaneously.

6.2.16 Assumed NHS costs per HAQ band.

The hospital costs assumed to be associated with HAQ score in each model are reported in this section. In summary a number of different sources are used, the data have been graphed in Figure 63. The data from MSD have been omitted as this is based on a more complex formula incorporating factors such as: age, disease duration and previous number of DMARDS and cannot be easily summarised. Pfizer and UCB purport to use the same source and the reason for the slight discrepancy is unclear.

Figure 63: A summation of the hospital costs assumed associated with each HAQ band



6.2.16.1AbbVie

AbbVie report that patients with more severe symptoms of joint disease are more likely to be hospitalised and may require surgical procedures such as joint replacement. Disease related hospital costs were estimated based on the Norfolk Arthritis Register (NOAR) database[238] and multiplied by National Reference costs.[239] The resource use for HAQ costs, assumed by AbbVie are given in Table 144.

Table 144: The hospital costs by HAQ band assumed by AbbVie

HAQ band	Total Cost
0.0 < 0.5	£167.41
0.5 < 1.0	£102.54
1.0 < 1.5	£364.68
1.5 < 2.0	£523.68
2.0 < 2.5	£1,246.26
2.5 < 3.0	£2,687.97

6.2.16.2BMS

BMS assume a cost per unit HAQI score, to incorporate costs for hospitalisation and joint replacement based on Malottki et al.[202] This was inflated to £1,245 per HAQ unit score to reflect 2011/12 prices.[205]

6.2.16.3MSD

Data from Brennan et al.,[155] were used to estimate the number of hospitalisations within the UK for every cycle of the model dependent on a number of characteristics, including TNFα inhibitor treatment which is used as a proxy for biologic DMARD treatment. The coefficients reported in Brennan are reproduced in Table 145. Costs of an inpatient day were estimated from NHS reference cost 2010-2011 (non-elective inpatient PA34B) with a mean of £517.

Table 145: Multivariate regression used by MSD to estimate the number of days of hospital stay

Independent variable	Coefficient
Intercept	0.2351
Utility at baseline	-0.5467
Age (years)	0.0078
Disease duration	0.0075
Previous number of DMARDs	0.0648
Anti-TNF	-0.062

6.2.16.4Pfizer

Direct annual costs of medical resource use, stratified by HAQ score, were uplifted[205] to 2011/12 prices from estimates provided by Kobelt et al, 2002,[240] derived from a UK observational database (The Early Rheumatoid Arthritis Study). Pfizer considered these data to be the most appropriate because it involved a multifaceted approach from the perspective of the NHS. Approaches to estimating costs in other identified sources were more restrictive in the items included. For example, Brennan et al.,[155] included only inpatient and monitoring costs.

These costs encompassed a broad range of resource use including hospitalisations, surgical interventions, outpatient visits, medication, and drug monitoring. The analysis did not include the costs of lost productivity, which have been used previously (220), which do not meet the NICE reference case (217). Alternative cost scenarios were considered in scenario analysis, including those used by Malottki et al.[202]

Table 146: The assumed annual costs of RA associated with HAQ score assumed by Pfizer

HAQ score interval	Mean annual costs
< 0.6	£1,138
0.6 < 1.1	£2,922
1.1 < 1.6	£1,938
1.6 < 2.1	£2,862
2.1 < 2.6	£3,153
≥ 2.6	£2,500

6.2.16.5Roche

It is assumed that patients often require inpatient care associated with RA in addition to the NHS resources utilised for drug administration and routine patient monitoring. Inpatient costs were calculated using the Norfolk Arthritis Register (NOAR) database. Inpatient hospitalisation was grouped by six HAQ score bands and are shown in Table 147.

Table 147: The inpatients visit by HAQ score assumed by Roche

HAQ Band at Registration	Patients in band *N*	Patients with inpatient stay		Number of days in hospital in the following 12 months			
		n	%	Mean	Median	IQR	Range
0.0 < HAQ score < 0.5	326	7	0.02	0.26	0	0-0	0-26
0.6 < HAQ score < 1.0	800	16	0.02	0.13	0	0-0	0-21
1.1 < HAQ score < 1.5	386	11	0.03	0.51	0	0-0	0-83
1.6 < HAQ score < 2.0	229	12	0.05	0.72	0	0-0	0-25
2.1 < HAQ score < 2.6	127	25	0.13	1.86	0	0-0	0-48
2.6 < HAQ score < 3.0	148	31	0.21	4.16	0	0-0	0-50

The method to incorporate resource utilisation in this analysis follows Kobelt and colleagues.[241,242]

Each HAQ score category was assigned an inpatient cost of £240.00 per day which is multiplied with the utilisation factor corresponding to each HAQ score category. The resulting inpatient resource utilisation values used in the analysis is summarised in Table 148. Note the Assessment Group have altered a typographical error in the last column (which read £62.40) and have changed the term per cycle (which is six months in the Roche model) to annual costs.

Table 148: The inpatient costs assumed by HAQ score by Roche

HAQ scores	0<0.5	0.6<1	1.1<1.5	1.6<2.0	2.1<2.6	2.6<3.0
Inpatient cost per year	£62.40	£31.20	£122.40	£172.80	£446.40	£99840

6.2.16.6UCB

Additional costs by HAQ-DI category, used by UCB were taken from a study by Kobelt et al.[240] In this study, a cohort of 916 patients in the UK was followed up for a mean of 7.8 years. Costs included the use of healthcare resources (direct) and loss of work capacity (indirect). Regression analyses were performed according to patients' HAQ-DI categories. Values were stated to be converted to Great British Pounds (GBP), although it is unclear why this was necessary given a UK cohort and inflated to a cost year of 2012.[205] The costs are applied at each cycle within the model, based on the HAQ score of each health state at each time-point. Only direct costs were included in the base case analysis, although the indirect costs were taken into account in a sensitivity analysis. The Assessment Group noted a slight discrepancy between the numbers reported by *UCB* and those used in the model. These are reported in Table 149.

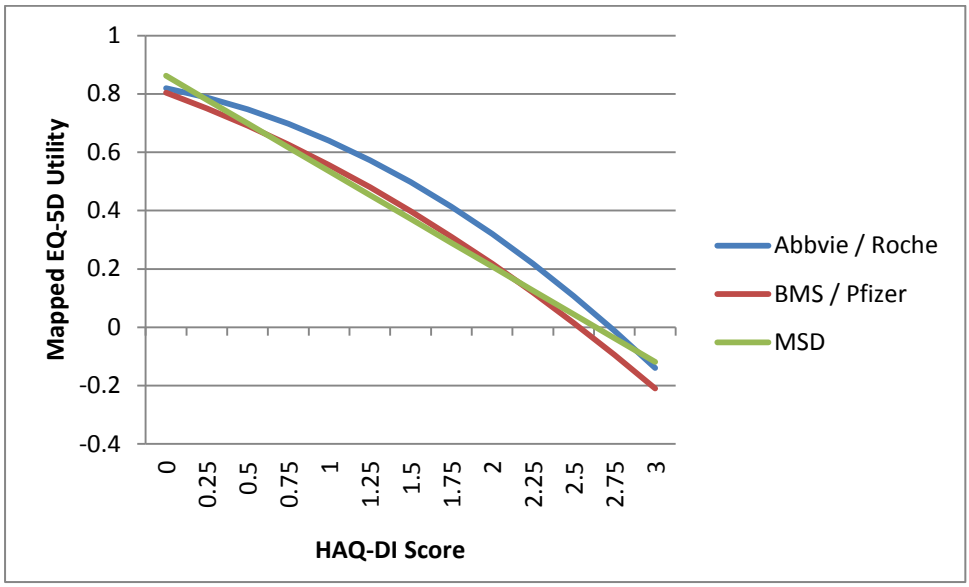
Table 149: Costs by HAQ-DI category

HAQ category	Direct costs (used in base case)	Direct Values used in the model	Total costs including indirect costs (used in sensitivity analyses)
<0.6	£1,102	£1082	£1,212
0.6 - 1.1	£2,827	£2,777	£5,000
1.1 - 1.6	£1,876	£1842	£4,902
1.6 - 2.1	£2,769	£2719	£7,388
2.1 - 2.6	£3,051	£2996	£10,105
≥2.6	£2,419	£2376	£9,781

6.2.17 Utility related to HAQ

This section details the utility values used in the models and a summary of the studies used in the submissions. Figure 64 provides a graphical estimation of the relationship between HAQ and utility assumed in the manufacturers' models. Data from UCB are not shown as UCB use EQ-5D data collected in the trial for ACR and EULAR categories and base utility around response categories.

Figure 64: The relationship between HAQ and utility assumed in the manufacturers' models



6.2.17.1AbbVie

The utility values used in the base case analysis by AbbVie were calculated using a equation reported within a poster[243] which maps between HAQ and EQ-5D, according to the UK specific EQ-5D tariff derived by Dolan.[244]

Both linear and non-linear equations for mapping HAQ to EQ-5D were presented. Using the linear utility mapping equation it is not possible for patients to achieve a negative utility, whereas the non-linear utility mapping equation relates a HAQ-DI score greater than approximately 2.7 to an EQ-5D score of less than zero.

Several studies examining quality of life in patients with RA indicate that severe RA health states can be associated with negative utility values indicating that the non-linear mapping equation more accurately represents the relationship between HAQ and quality of life in patients with very severe RA and functional impairment.[245-248] This is supported by Ducournau[243] and colleagues who report that the inclusion of a non-linear term resulted in an improved fit, and that the non-linear term was a significant coefficient. Previous analyses have also suggested a non-linear relationship between HAQ-DI and utility in RA patients.[249]

The main report provides no details whatsoever on issues required to judge the appropriateness or otherwise of the statistical models. No details of how uncertainty in the estimates was propagated in the model, if at all, is provided. No details are provided either on the data used to estimate the relationship, or the performance of the models in that dataset. the appendix reports an additional

model from the same dataset that also includes age as a covariate, though the coefficient is quite small. No details are given as to why this was not used.

The provided poster of the Ducournau et al. reference [243] gives little additional detail. The overall numbers of patients reported in the trials are reported but no details on the numbers of observations used in the statistical analyses are provided.

The quadratic mapping equation was therefore selected for the base case analysis while the linear mapping equation was examined in sensitivity analyses.

The model used to calculate utility values in the base case analysis is:

$$\text{EQ-5D} = 0.82 - 0.11*\text{HAQ-DI} - 0.07*\text{HAQ-DI}^2$$

In order to investigate the impact of the quadratic term on the results of the cost-effectiveness analysis, a sensitivity analysis was conducted using the linear regression model reported by Ducournau et al.

The linear regression model used in the sensitivity analysis was:

EQ-5D = 0.89 – 0.28* HAQ-DI

6.2.17.2BMS

The HAQ score is converted into a utility value using the mapping algorithm used by Malottki et al (2011[202]):

$$EQ - 5D = 0.804 - 0.203 \times HAQ - 0.045 \times HAQ^2$$

The report does not state whether the parameter uncertainty in this regression was taken into account (e.g. by using the variance/covariances) or if the error terms were also included in order to reflect the additional heterogeneity in the patient level sample. BMS consider a sensitivity analysis that uses an alternative linear regression from Malottki et al.,[202] which excludes the quadratic term.

Malottki et al.,[202] report this regression as "Birmingham analysis of dataset from Hurst.[213]" Only confidence intervals on the coefficients are reported, not the covariances. Hurst et al is a study from

1997 of 233 RA patients. Note that in their regression work they also find that pain as well as HAQ score are significant predictors of EQ5D. No detail of model fit is provided.

6.2.17.3MSD

The quality of life equations used in the MSD submission is provided in Table 150 with reference to Chen et al.[113] It is not clear if the uncertainty, and covariance in the estimated coefficients was considered in sensitivity analysis.

Table 150: The quality of life equations used in the MSD submission

State	Regression estimate	SE
Constant	0.862	0.034
HAQ Coefficient	-0.327	0.0201

6.2.17.4Pfizer

The primary analysis in all populations used the algorithm derived by Malottki et al.[202] The equation for this is:

$$EQ - 5D = 0.804 - 0.203 \times HAQ - 0.045 \times HAQ^2$$

Pfizer undertook a systematic review of mapping studies in RA (section 4.3.3.2.2). Many studies were discarded because the studies were conducted using patients from a non UK patient population.

The Assessment Group comment that there is no requirement in the NICE Methods Guide (either version 2008[250] or 2013[251]) for patients to be selected from the UK, nor is there any obvious theoretical reason why this should be the case. The Guide requires that the valuations of health states described by these patients are drawn from the UK, and in RA this would be appropriately achieved by using the UK tariff of the EQ-5D instrument.

The use of this criterion in their selection of studies is therefore misguided.

Three studies remain in Pfizer's Table 50: Hurst et al.,[213] (and the subsequent fitting of a quadratic equation to the same data in Malottki et al.,[202]), Bansback et al.,[252] and Hernandez et al.[253] The submission uses the Malottki equation as the base case and the original Hurst et al regression in scenario analysis. Table 50 provides their rationale for discarding the Bansback et al and Hernandez et

al studies. Further details are given for each of these studies below but some key points require addressing here:

The reporting of the characteristics of these three studies is misleading:

- Bansback et al is discarded on the basis that it includes both UK and Canadian patients. However, it is clearly stated that the UK tariff is applied to the EQ-5D analysis and therefore the criticism is misguided.
- Hurst is claimed to have "Relevant summary statistics reported" whereas Hernandez et al is "The sample of the statistical analysis is not clearly stated" In fact the sample of patients is fully described in the accompanying clinical trial paper referred to in the manuscript. Critical to the selection of an appropriate statistical model is the distributional characteristics of the dependent variable – this is not reported in Hurst et al.[213]
- Doubt is cast on the Hernandez et al results since the patients are defined as having early RA at baseline which may not be generalizable to more established disease. However Hurst et al; comprises a mixed population of both early and late stage disease, there is a clear relationship between patient degree of functional severity and disease duration (Table I), but there is no statistically significant relationship between duration and EQ5D (Table V) and nor does it feature in any of the regression analyses (though the study may be too small to detect any effect). It is therefore difficult to see how the same criticism of the relevance of the Hernandez et al paper to the current decision problem does not also apply to the Hurst et al analysis.

- The most important issue is stated as VAS pain is not estimated over time, therefore did not support the current model approach. For clarity, the Hernandez et al work did include pain score as a separate covariate alongside HAQ because a much more powerful model results (this was also found by Hurst et al). It is the Pfizer cost effectiveness model that does not consider pain and therefore was considered incapable of using the results, though of course a HAQ based model could be adapted to also include the assessment of pain.

6.2.17.5Roche

The method to assign utility weights to simulated patients and to derive QALY outcomes in the model is the same as used in our TCZ and MTX combination therapy NICE submission (2011). The analysis uses a mechanism of mapping utility from patient HAQ score. This technique is also similar to previously published cost-utility studies and reimbursement submissions of biologic treatments in RA [Bansback 2005], [Brennan 2004]. A description of the methods is presented in the Appendix.

The base case analysis uses a quadratic equation to map HAQ to utility:
$EQ5D = 0.82 - 0.11*HAQ – 0.07 * HAQ^2$ *(p-value < 0.0001; for both coefficients)*

The estimates come from two phase 3 trials (OPTION[126] and LITHE[254]). The numbers within the analyses are not reported, nor is any information on the distribution of the data. Only p-values are given for the estimated coefficients: no standard errors or confidence intervals. There is no information that allows one to judge the fit of the model to the actual data. Roche compared HAQ and HAQ^2 models, and one with age (not age^2). Riche found the age coefficient was very small (surprisingly and not consistent with most other findings that EQ5D is strongly related to age) so dropped these analyses.

The model with $HAQ^2$is selected because it has a better fit, but this is not assessed using any kind of penalised likelihood test. In fact their chi-squared test is equivalent to the p-value on the HAQ^2 coefficient and not appropriate for comparing models. This is important because adding an additional covariate will improve fit, but it is not good practice to simply improve fit by adding covariates: this risks losing generalisability.

In sensitivity analysis three alternatives are tested, though it is not reported where they have come from except the last which is based on Hernandez Alava et al.,[253] however, the uncertainty in the coefficients were not used.

6.2.17.6UCB

UCB have a different model structure to the others in that they are basing it predominantly around response categories within a Markov framework.

This is done in several steps:

Critically, in the severe disease population:

i) Initial response is defined in terms of ACR category and a mean EQ5D improvement estimated from a linear regression using trial data from the RAPID[129,130] RCTs. No information on key

statistics such as fit, sample was provided making it impossible to judge appropriateness or otherwise. It was unclear how PSA implemented nor how additional covariates were selected or used.

ii) Continued improvement in HAQ is converted to EQ-5D score from Bansback et al 2006.[255]

In the moderate disease population:

i) Initial response is defined in terms of EULAR category. Regression analysis is used to estimate EQ5D change by EULAR category based on data from the CERTAIN study.[71] No details are given. Different estimates are made according to the treatment strategy i.e. this is not assumed to be a relationship that is independent of treatment.

ii) The same Bansback et al. estimate is then used for other elements of the model.

Summary of studies used in submissions:

Hurst et al.,[213] and Malottki et al. [202] are used as the base case by BMS, MSD and Pfizer, and used in sensitivity analysis by tocilizumab.

Hurst et al. recruited 233 patients with RA from Scottish RA outpatient departments. They also aimed to recruit more severe patients from inpatients and via GPs and residential care. They failed to recruit desired numbers of patients into functional severity class 4. The paper reports 3-month follow up data and compares it to baseline data. There is no combined analysis.

The paper does not display the distribution of HAQ or EQ5D tariff score.

Linear regression was used to estimate EQ-5D as a function of HAQ and other covariates, with stepwise regression used to select variables.

The reported model for EQ-5D at three months includes HAQ, HAQ mood score, pain VAS, disease activity and ESR.

The simple linear model that only uses HAQ as an explanatory variable is not reported in the Hurst et al paper but is reported in Chen et al.,[113] who were supplied with the Hurst et al dataset. They report no details about the sample used (whether this was identical to that reported in the paper), its spread, how repeated observations were dealt with, the distribution of the explanatory variable and its range, how the model performed in terms of fit, bias, predictions outside the feasible range. No details of the uncertainty in the estimated coefficients is provided by Chen et al. Malottki et al.,[202] is an update from the same group and they similarly report no details on any relevant information required to make a judgement as to the appropriateness or otherwise of the statistical model. The only change made is the addition of a quadratic term.

6.2.18 The assumed costs and disutilities associated with adverse events

The assumptions regarding adverse events within each submission is detailed in this section. In summary, only two of the six manufacturers explicitly included the costs of SAEs within the submission. These were AbbVie (£4568 per episode) and Pfizer (£1497 per episode) with Pfizer only examining this within a sensitivity analysis.

Only Pfizer included disutility associated with a serious adverse event, assuming a disutility of 0.156 for a period of 28 days, equating to approximately a 0.012 QALY loss.

Data on the rates of adverse events are summarised in the section entitled 'Time to discontinuation of treatment'.

6.2.18.1AbbVie

AbbVie taken into account serious infections are in the model, citing the important consequences arising in terms of resource utilisation following serious infection. It was assumed that mild or moderate AEs had minimal impact on a patient's quality of life and have minimal cost implications. The baseline annual risk of serious infections under treatment with non-biologic DMARDs was extracted from a prospective observational study using BSRBR[256] data and assumed to be the same for all non-biologic DMARDs.

Baseline values for conventional DMARDs were extracted from BSRBR data, the risk of serious infections for biologic treatments being adjusted through risk parameters derived from a meta-analysis of safety parameters from clinical studies of biologics used in majority in RA.

Risk of serious infections under treatment with biologics was derived using odds ratios of serious infections of biologics versus control treatment derived from a systematic review and meta-analysis of 160 randomised clinical trials by the Cochrane collaboration (erroneously referenced as Hetland et al[225]). Although the meta-analysis includes trials of biologics in indications other than RA (but excluding HIV), the majority of trials have been conducted in RA, and AEs are considered to happen irrespective of indication.

To calculate the risks of serious infections under treatment of biologics the baseline risk for DMARDs was converted to odds, the odds for each respective biologic were calculated using the odds ratios which were subsequently converted to risks. Serious infections risks employed in the base case analyses as well as odds ratios employed to estimate these are displayed in Table 151. The Assessment Group comment that the odds ratios shown in Table 151 do not match Figure 4 in the most recent version of Singh et al.[257]

Table 151: The risk of serious infections assumed in the AbbVie model

Treatment	Risk	Odds Ratio[b]
DMARDS (MTX, MTX+HCQ, SSZ+HCQ, LEF, SSZ, CYC, HCQ	0.031493[a]	Reference
ABA (+/-MTX)	0.018198	0.57
ADA (+/-MTX)	0.035140	1.12
ETA (+/-MTX)	0.033320	1.08
INF (+/-MTX)	0.045027	3.51
RTX (+/-MTX)	0.030578	1.06
GOL (+/-MTX)	0.040259	1.29
TOC (+/-MTX)	0.048867	1.45
CER (+/-MTX)	0.102444	0.97

ABT = abatacept; ADA = adalimumab; CTZ = certolizumab; CYC = ciclosporin; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; IFX = infliximab; LEF = leflunomide; MTX = MTX; RTX = rituximab; SSZ = sulfasalazine; TCZ = tocilizumab

Source:

a. Galloway 2011[256]

b. Singh et al. 2011[257]

A sensitivity analysis was conducted setting the risk of adverse events for etanercept, adalimumab and infliximab to 0.03767, 0.04075 and 0.04075 respectively (higher), based on the Galloway BSRBR data. Data are not available for other biologics from this BSRBR analysis.

The cost of serious infections was obtained from NHS reference costs and was assumed to be £4,568.38 per episode of care corresponding to the elective spell tariff of inflammatory spine, joint or connective tissue disorders with major complications (HD23A). The mean length of stay corresponding to the elective spell tariff was 8.2 which was comparable to the median of seven days suggested by Galloway[256] and colleagues used to derive baseline AE risks. Despite commenting on the effect on patients on serious infections no disutility associated with serious AEs were used.

6.2.18.2BMS

The probabilities of adverse events used within the BMS model are shown in Table 152. The source for these data was not provided in the submission. AEs only result in discontinuation of present treatment. There are no cost implications, not explicit utility implications.

Table 152: The assumed probability of adverse events used in the BMS models

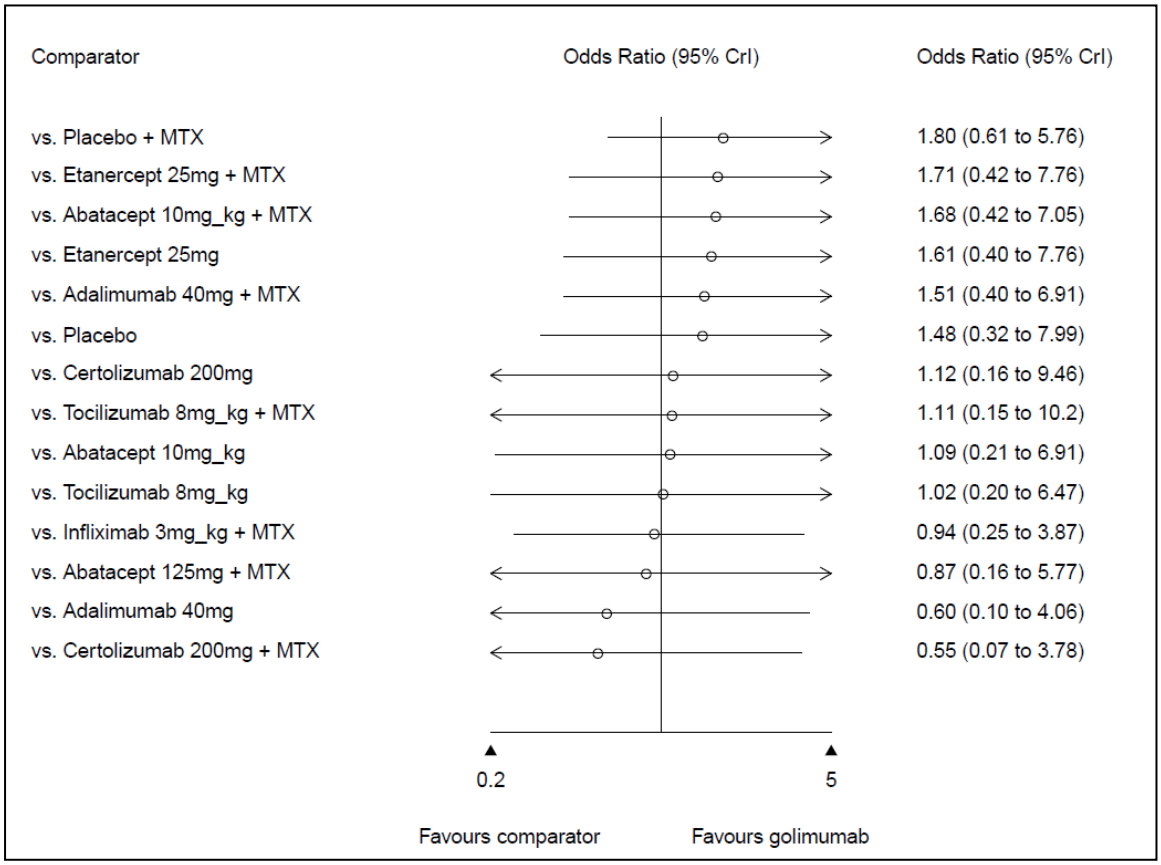
	At Month 6/Week 24
Treatment	**Probability of adverse event**
IV abatacept	0.023
SC abatacept	0.016
Adalimumab	0.041
Etanercept	0.030
Infliximab	0.086
Tocilizumab	0.041
Golimumab	0.020
Certolizumab pegol	0.096

DAS28 change from baseline is assumed to be normally distributed and is sampled for each patient. IV: intravenous; DAS: Disease Activity Score; SC subcutaneous; SD: standard deviation.

6.2.18.3MSD

Adverse events are incorporated into the model based on the proportion of patients who discontinue treatment due to adverse events in the first 24 weeks. (Figure 65)

Figure 65: Odds Ratio of discontinuations due to adverse events in cDMARD experienced patients assumed by MSD



Adverse events are assumed to be class related therefore the costs and utility outcomes are assumed to be equivalent between the biologic DMARDs. This rate does not appear to be tabulated in the submission. No costs or disutility associated with adverse events are included in the MSD model although MSD comment that it is possible that adverse event disutility associated with rheumatoid arthritis treatment was already incorporated into the mapping equation from HAQ to utility.

6.2.18.4Pfizer

Pfizer's base case did not model AEs, with the manufacturer noting that several manufacturer's submissions for NICE appraisals RA have not modelled AEs.[204,209,210]

A scenario analysis including serious infections was performed. The medical resource use estimates derived from data presented by Kobelt et al.,[240] contain costs of hospitalisations, and therefore AEs were not concluded within the primary analysis in order to avoid any 'double-counting' of these costs (218). Serious infections were selected for the model as opposed to, for example, serious adverse events [SAEs] as HRQL consequences associated with infection in alternative populations has been well documented.[258] Following a serious infection, the Summary of Product Characteristics for all

bDMARDs stipulates treatment cessation, which is not the case for other SAEs. Pfizer argue that the treatment of other AEs is unlikely to utilise a significant amount of medical resources or costs to the NHS.

Pfizer performed a network meta-analysis to estiamte hazard ratios of serious infection (SI) vs cDMARDs. These hazard ratios were applied to the risk of serious infection for MTX,[259] estimated from NMA, to provide the cumulative probability of serious infection and are replicated in Table 153. Golimumab and Infliximab were assumed to have the same rate of serious infection as adalimumab as all have a similar mode of action. Rituximab was assumed to have the same rate of serious infection as Tocilizumab as both are intravenously administered treatments.

Table 153: Hazard Ratio of serious infection vs cDMARDs presented by Pfizer

	Severe DMARD-IR		
	Fixed effect NMA		
	Median OR	**Lower 95% CrI**	**Upper 95% CrI**
ABT	1.282	-4.440	6.850
ADA	2.945	0.075	9.150
CZP	1.540	-4.007	7.334
CIC†	0.000	0.000	0.000
ETN	1.108	-3.377	7.202
ABS	0.556	-7.481	8.323
GOL‡	2.945	0.075	9.150
INF‡	2.945	0.075	9.150
LEF†	0.000	0.000	0.000
MTX	0.000	0.000	0.000
PC†	0.000	0.000	0.000
RTX§	1.213	-1.334	6.019
SUL†	0.000	0.000	0.000
TOC	1.213	-1.334	6.019
Comb cDMARD†	0.000	0.000	0.000

Abbreviations: ABT, abatacept (iv);ABS, abatacept subcutaneous; ADA, adalimumab; cDMARD, conventional disease modifying antirheumatic drug; comb cDMARD, combination conventional disease modifying antirheumatic drug; CIC, ciclosporin; Crl, credible interval ; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; LEF, leflunomide; NMA, network meta-analysis; OR, odds ratio; PC, palliative care; TNF-α, tumour necrosis factor alpha; RTX, rituximab; SUL, sulfasalazine; TOC, tocilizumab; TX, treatment; † assumed to be equivalent to MTX ; ‡assumed to be equivalent to adalimumab; § assumed to be equivalent to tocilizumab.

Cost of AEs

Within the adverse events scenario analysis, the cost of serious infection was assumed to be £1,497 based on relevant NHS costs, weighted by inpatient activity.[203] Relevant HRG codes were identified based on Lekander et al, 2010.[167] Conservatively the without complications and contraindications HRG costs were used.

Table 154: Costs of serious infection (using in scenario analysis only)

Currency Code	Currency Description	Activity	National Average Unit Cost
WA03Y	Septicaemia without CC	595	£1,752
DZ23C	Bronchopneumonia without CC	320	£1,438
LA04F	Kidney or Urinary Tract Infections with length of stay 2 days or more without CC	11601	£1,408
PA16B	Major Infections without CC	3866	£2,623
DZ22C	Unspecified Acute Lower Respiratory Infection without CC	3969	£1,079
DZ21K	Chronic Obstructive Pulmonary Disease or Bronchitis without NIV without Intubation without CC	10053	£1,266
Weighted average cost			£1,479

Abbreviations: CC, complications; NIV, Non-invasive ventilation; source: NHS reference costs schedules 2010-11 (296)

Serious infections were assumed to persist for 28 days and confer a disutility 0.156 during that time.[258]

6.2.18.5Roche

The economic model does not assume a difference in adverse events between biologic treatments and assumes neither associated costs nor utility decreases associated with adverse events

6.2.18.6UCB

The costs and outcomes associated with adverse events were not included within the UCB model as it was assumed that all biologic therapies had similar safety profiles.

UCB comment on the robustness of Cochrane collaboration review of the adverse events of biologics regarding the adverse events of certolizimab pegol.[260] This comment is marked academic-in-confidence.

[redacted]

6.2.19 Mortality Associated with RA

The assumptions regarding the effect of RA (and HAQ score) on mortality is detailed for each submission.

In summary there is no consensus of the most appropriate approach although four submissions assume that the relative risk of mortality per HAQ score can be determined from a paper by Wolfe et al.[261]

These data (as will be detailed in the methodology used by the Assessment Group) are dated and have been superseded, furthermore these data do not indicate whether the mortality risk is reversible following treatment which reduces a patient's HAQ.

Two submissions have assumed standardised mortality rate for patients with RA that is assumed independent of HAQ. Pfizer have commented that the impact of mortality on cost-effectiveness ratios have been shown to be marginal due to discounting.

6.2.19.1AbbVie

The submitted model includes general population mortality rates based on UK life tables. However, mortality rates are assumed to be affected by HAQ score. The effect of HAQ on mortality was expressed as a hazard ratio of 1.33 per unit increase in HAQ score for both males and females taken from Wolfe et al.[261] Sensitivity analysis varied the hazard ratio using values 1.00 and 1.88.

To implement this general population mortality risks (2009) were derived by fitting a Gompertz function to the data from gender specific UK life tables. The Gompertz function describes the exponential increase in mortality rates with increasing age in the absence of high rates of age-independent mortality.

$$S_t = e^{\left[-\frac{(e^{\gamma t}-1)e^{\lambda}}{\gamma}\right]}$$

Table 155: The assumed Gompertz fit to standard mortality data within the AbbVie model

	illMean	**SE**	**Rho**
Females			
Lambda	-10.688847	0.05353145	-0.92256954
Gamma	0.0951409	0.00077774	
Males			
Lambda	-9.6568365	0.05960999	-0.92256954
Gamma	0.08567803	0.00086605	

SE = standard error

The effect of HAQ on mortality was expressed as a hazard ratio of 1.33 per unit increase in HAQ score for males and females.[18] Two major assumptions are made:

1. The hazard ratio was assumed to be linear in the HAQ.
2. A change in the HAQ has an immediate effect on the expected mortality (i.e., not only the baseline HAQ).

AbbVie present illustrative curves for mortality dependent on HAQ scores, which are reproduced in Figures 66 and 67.

Figure 66: An illustrative mortality survival curve presented by AbbVie for males

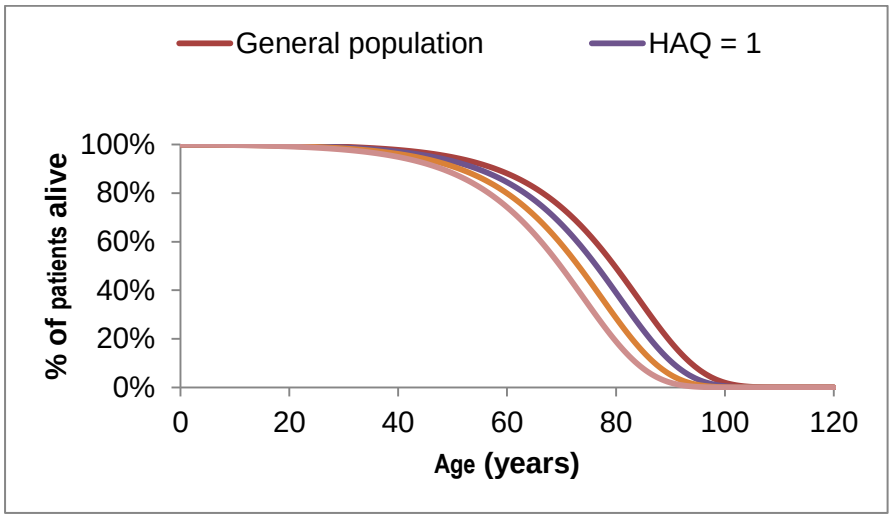
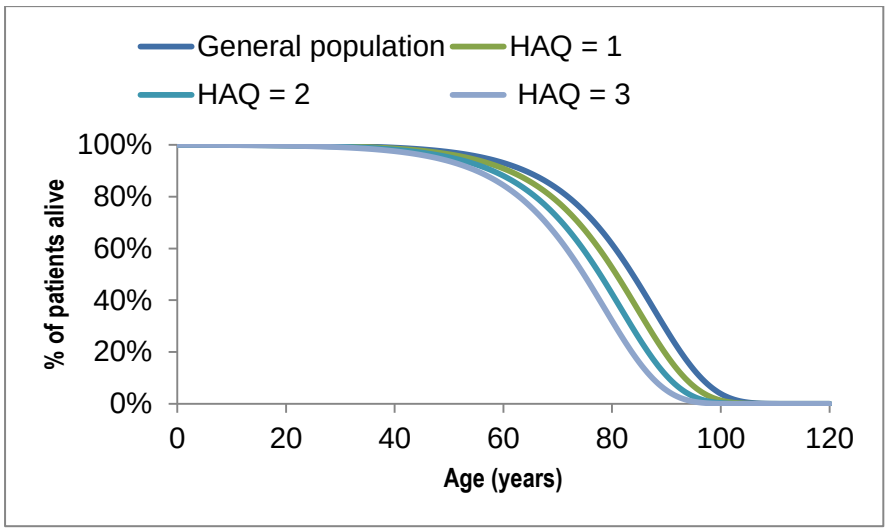


Figure 67: An illustrative mortality survival curve presented by AbbVie for females



The Assessment Group comment that no goodness of fit values for the Gompertz model compared with the life table data were presented.

6.2.19.2BMS

The expected age at which a patient dies is based on age, gender and HAQ score and is recalculated every time the HAQ score changes. Once the age of the patient exceeds their assigned 'age at death', the patient dies. The age at death is calculated using conditional probabilities as follows replicating the methodology used by Barton et al.[152]

Let a and b be the gender-specific survival probabilities for ages x and y respectively, for a member of the general population. The probability p that a patient of age x will survive to the age y is $p = \frac{b}{a}$.

However, it is assumed that there is an increased risk of death for patients with RA, modelled as a HAQ mortality ratio of 1.33 per unit HAQ.[261] Therefore the probability p that a patient of age x will survive to the age y is $p = (\frac{b}{a})^{1.33 \times HAQ}$. This can be rearranged to give $b = a \times p^{\frac{1}{1.33 \times HAQ}}$.

The model looks up the survival probability for the current age of the patient for a, and uses a random number between 0 and 1 for p. The age at death is then calculated by looking up the age with the corresponding survival probability closest to b.

6.2.19.3MSD

National life tables for the UK[262] were used to obtain age dependent mortality rates. Furthermore, the proportion of males and females recruited in the infliximab trials were used to estimate a weighted average mortality risk by sex. The mortality rates taken from national life tables were annual rates. They were adjusted to the model cycle length rate using the following equation:

$$r = -[\ln(1 - P)]/t$$

The cycle rates were transformed into transition probabilities using the following equation:

$$p = 1 - \exp\{-rt\}$$

A standardised mortality ratio of 1.65 is used in the model although not referenced in the report. On examination of the Excel spreadsheet indicates that this comes from Chenhata et al 2001 and is not HAQ dependent.

6.2.19.4Pfizer

Pfizer identify a number of economic evaluations that have assumed either a general risk of mortality associated with RA which is independent of disease severity measures[155,165,167,175,210,263,264] or have expressed mortality as dependent on functional status (typically as expressed by HAQ).[152,166,171,186,204,209,265,266]

The Pfizer model adopts the former approach, assuming an age-gender specific standardised mortality ratio (SMR) from Brennan et al, 2007[155], who report age and gender specific standardised mortality ratios for a UK population.

This approach avoids the implicit assumption that mortality rates would differ between treatment sequences, but Pfizer report that evidence suggests that this approach may be conservative.[267,268]

However Pfizer also note that assumptions on mortality have little impact on the cost-effectiveness ratios due to discounting citing both NICE TA130[215], Vera-Llonch et al, 2008.[175]

Pfizer comment that the original data used to estimate the function relating HAQ to mortality is now nearly 20 years old and from a non-UK population.[261] Therefore, the standardised mortality ratios used by Brennan et al, 2007[155] were applied to life-tables for England and Wales.[262] These values are replicated in Table 156.

Table 156: The assumed standardised mortality ratios assumed by Pfizer

Age	Female	Male
0 - 24	2.0	2.0
25 - 64	1.8	1.6
65 - 101	1.5	1.3

6.2.19.5Roche

The probability of death used within the Roche model is based on an adjusted life table provided by the Office of National Statistics [Office of National Statistics 2010]. An RA risk multiplier related to each simulated individual's HAQ score is applied at each cycle based on work by Wolfe and colleagues [Wolfe 1994[261]], who studied the relationship between HAQ score and early mortality. Wolfe et al concluded that a relative risk of 1.33 (CI 1.099 – 1.61) was associated with each HAQ score point increase. The formula for converting this finding into an adjusted mortality risk (1.33HAQ) was derived from Barton et al. [Barton 2004[152]].

6.2.19.6UCB

The probability of all-cause mortality was derived from age- and gender-specific mortality rates for the general population from the Government Actuary Department, adjusted by HAQ-DI score. The base case estimate of relative risk of death of 1.330 per HAQ-DI unit (95% CI 1.099 to 1.610) was taken from a 35-year cohort study of 3,501 RA patients in Canada.[261] The starting mortality rate in cycle 1 was adjusted to the age and gender distribution of the model population and further adjustment was made in each model cycle to represent the increased risk of death as patients became older.

Examination of the UCB model suggests that an exponential distribution is fitted to the life table data, then a relative risk is applied. The exponential fits performed by the Assessment Group are shown in Figure 68 for females and Figure 69 for males. It is seen that the R^2 value is in excess of 0.99

Figure 68: The general mortality rate for females assumed by UCB, with an exponential fit to these data points

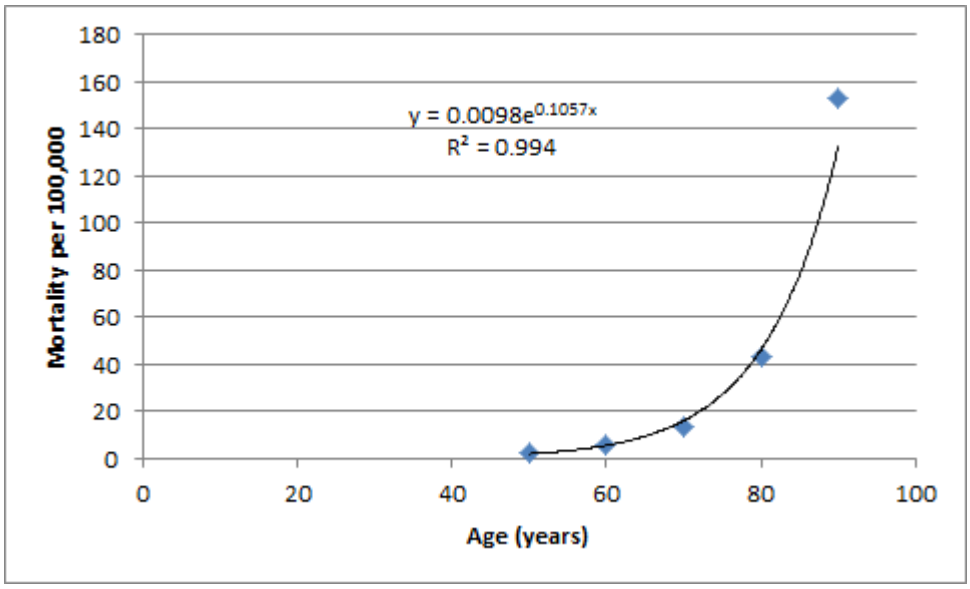
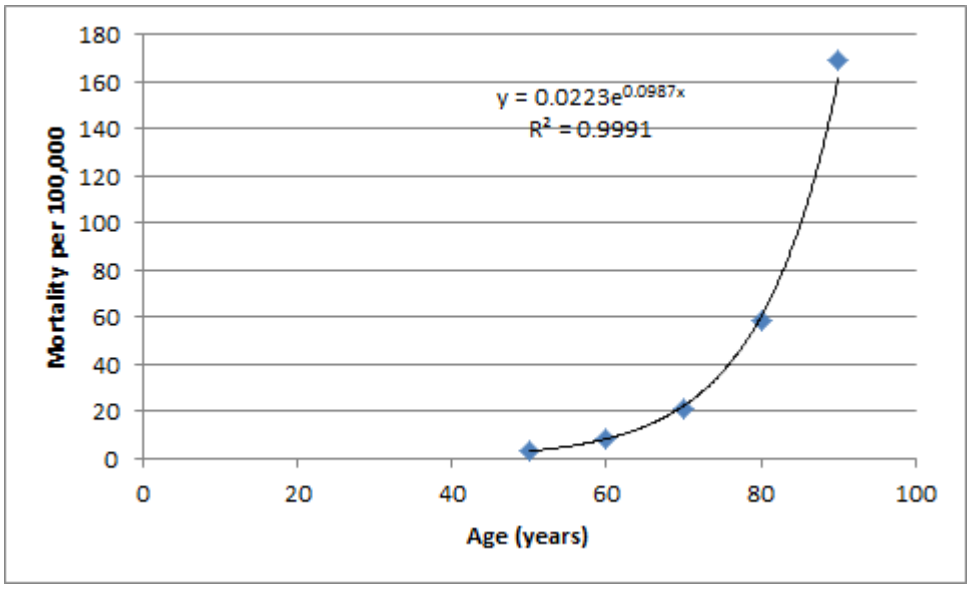


Figure 69: The general mortality rate for females assumed by UCB, with an exponential fit to these data points



6.2.20 Cost-effectiveness results within the manufacturers' submission

This section details the cost-effectiveness results reported by the manufacturers within their base cases for each of the analyses undertaken. Typically a large number of sensitivity analyses and descriptive features, such as cost-effectiveness acceptability curves, (CEACs) cost-effectiveness planes, and scatterplots are presented by the manufacturers. The Assessment Group has selected reported the key information for brevity reasons although has endeavored to report the salient conclusions.

Within the section the following terminology has been used to aid understanding; Analyses 1 to 6 represent the decision problems within the NICE scope.

Analysis 1: Population 2 in combination with MTX
Analysis 2: Population 3 in combination with MTX
Analysis 3: Population 1 in combination with MTX
Analysis 4: Population 2 monotherapy
Analysis 5: Population 3 monotherapy
Analysis 6: Population 1 monotherapy
Analysis 7: General RA Population who can receive MTX
Analysis 8: MTX intolerant or contraindicated RA population

Table 157 provides a summary of each manufacturer's interpretation of the cost-effectiveness analyses for their product. Where a manufacturer did not undertake an analysis the cell is blank,

otherwise the Assessment's Group conclusion of the manufacturers' interpretation of the cost-effectiveness is shown. Three manufacturers (AbbVie, BMS and MSD) have stated that the bDMARDs have similar cost-effectiveness ratios and should be analysed jointly; Pfizer and UCB make preferential statements about their interventions, whilst Roche have conducted an analysis that consists only of adding tocilizumab as a monotherapy as first-line before a non-NICE recommended sequence. There are few clear patterns exhibited in Table 157 except that all manufacturers believe their product in cost-effective in Analysis 1, and all bar UCB believe their inteventions are cost-effective in Analysis 2. It is commented that the Analysis 1 undertaken by UCB omitted a comparison against a cDMARD only strategy. Given that the remaining manufacturers often commented that the ICERs between population 2 and population 3 were similar, it is possible that UCB would have estimated bDMARDs not to be cost-effective in population 3 were the correct comparison to be made.

These results will be affected by the consideration (or not) of patient access schemes, which are in place for abatacept iv; abatacept sc; certolizumab pegol; golimumab; and tocilizumab. AbbVie do not consider current patient access schemes. None of MSD, Pfizer and UCB include patient access schemes for tocilizumab or abatacept as these are commercial-in-confidence. BMS and Roche use patient access schemes for all relevant drugs in their analyses.

Table 157: A summary of each manufacturer's interpretation of the cost-effectiveness analyses for their product assuming a cost per QALY threshold of £30,000

			Manufacturer						
Analysis	Decision Problem	Scope	AbbVie (ADA)	BMS (ABT)	MSD (GOL)	MSD (IFX)	Pfizer (ETN)	Roche (TCZ)	UCB (CTZ)
1	Population 2 in combination with MTX	✔	CE (Group)		CE (Group)	CE (Group)	Most CE		Most CE
2	Population 3 in combination with MTX	✔	CE (Group)				CE (Sole)		Not CE
3	Population 1 in combination with MTX	✔	Not CE				Not CE		
4	Population 2 monotherapy	✔	Not CE				Most CE		Most CE
5	Population 3 monotherapy	✔	Not CE						Not CE
6	Population 1 monotherapy	✔	Not CE						
7	General RA Population who can tolerate MTX [Δ]			CE (Group)	CE (Group)	CE (Group)			
8	MTX intolerant or contraindicated RA population †							CE(Sole)	

Shaded cells indicate the intervention is not licensed in this population; blank cells indicate an analyses was not conducted
ADA = adalimumab; ABT = abatacept; GOL = golimumab; IFX = infliximab; ETN = etanercept; TCZ = Tocilizumab; CTZ = certolizumab pegol; MTX = MTX. iv = intravenous; sc = subcutaneous
[Δ] In essence, analyses 1 and 2 combined † In essence, analyses 4 and 5 combined.

CE (Group) denotes the manufacturer is stating that the bDMARDs have similar incremental cost-effetive ratios and that all are cost-effective compared with cDMARDs alone
CE (sole) denotes the manufacturer did not consider other bDMARDs within the analyses
Most CE denotes the manufacturer is stating that their intervention is the most cost-effective bDMARD and that it is cost-effective compared with cDMARDs alone
Not CE denotes the manufacturer does not claim the intervention is cost-effective compared with cDMARDs.

6.2.20.1AbbVie

Within the AbbVie submission the Assessment Group notes that abatacept sc has not been included, that the responder criterion is ACR50 and that the patient access schemes in place for some interventions have not been included.

Despite performing probabilistic sensitivity analyses (PSA) AbbVie present deterministic results in the base case tables.

The incremental cost-effectiveness analyses are shown in Table 158 for Analysis 1 and Table 159 for Analysis 2. CEACs from the probabilistic analyses are provided in Figure 70 for Analyses 1 and Figure 71 for Analyses 2.

Table 158: Incremental cost-effectiveness ratios for Analysis 1 as reported by AbbVie

		Total		Incremental		ICER	
Sequence	**Technology**	**Costs**	**QALYs**	**Costs**	**QALYSs**	**Versus DMARDs**	**Incremental**
1	DMARDs	£36,636	1.747				
8	TOC+MTX	£94,128	4.433	£57,492	2.686	£21,405	Ext Dominated
4	INF+MTX	£97,366	4.981	£60,731	3.234	£18,781	Dominated
7	ABA+MTX	£116,143	5.036	£79,508	3.289	£24,172	Dominated
6	GOL+MTX	£95,754	5.107	£59,118	3.360	£17,594	Dominated
2	ADA+MTX	£94,618	5.230	£57,983	3.483	£16,650	Ext Dominated
5	CER+MTX	£97,091	5.288	£60,455	3.541	£17,071	Dominated
3	ETA+MTX	£96,785	5.377	£60,149	3.630	£16,571	£16,571

Figure 70: Cost Effectiveness Acceptability Curves for Analysis 1 provided by AbbVie

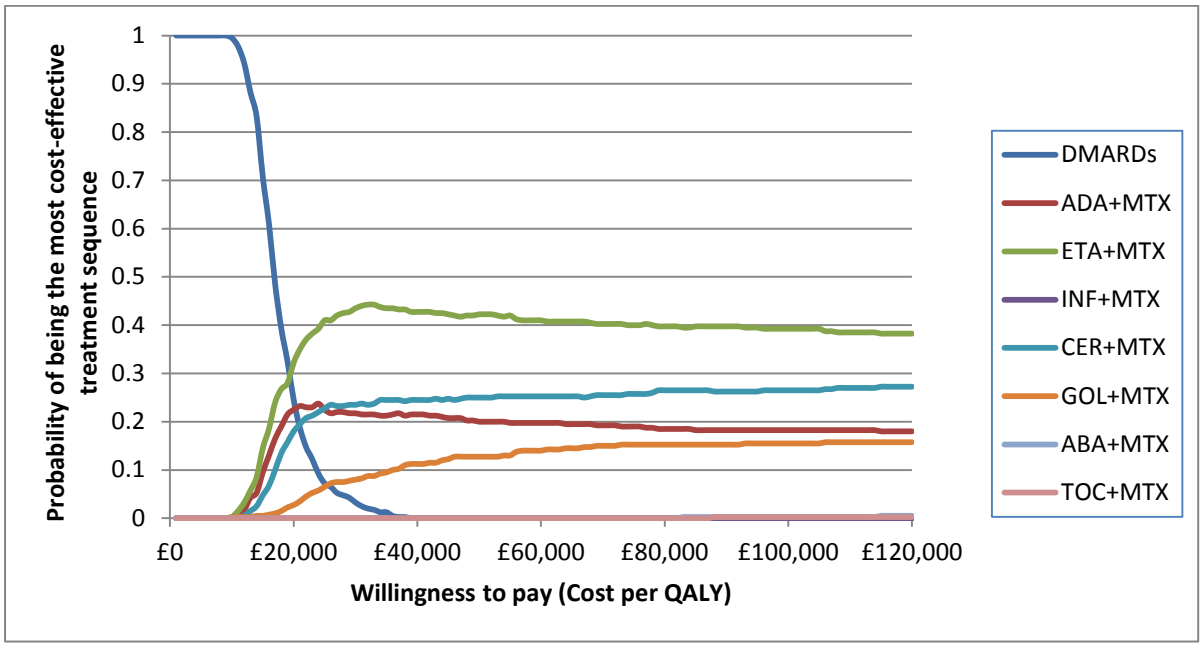
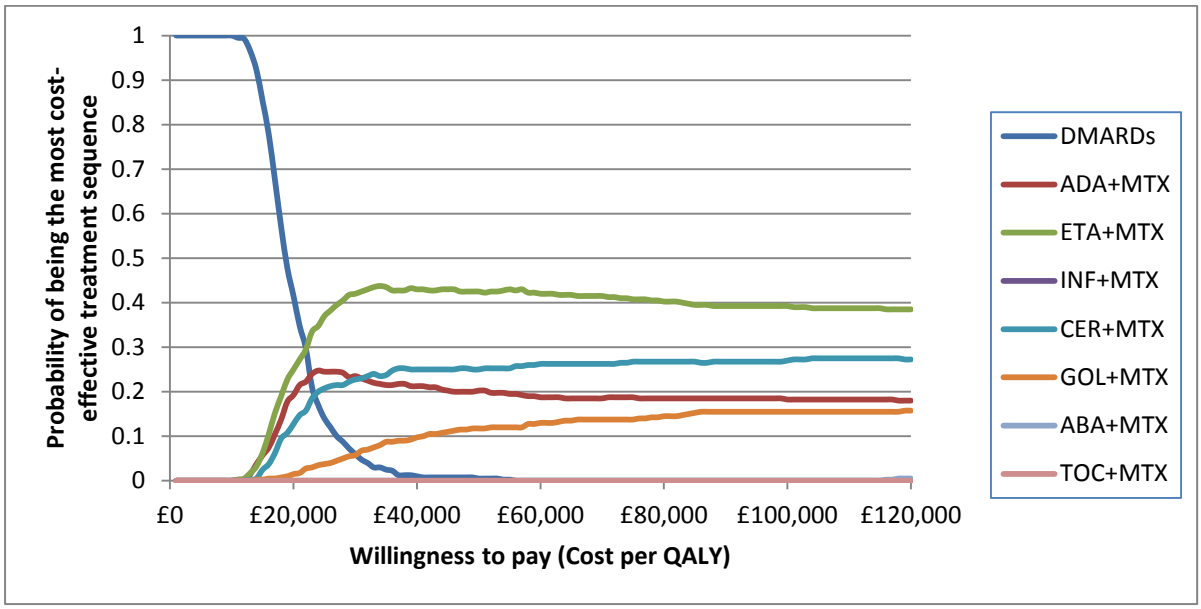


Table 159: Incremental cost-effectiveness ratios for Analysis 2 as reported by AbbVie

		Total		Incremental		ICER	
Sequence	**Technology**	**Costs**	**QALYs**	**Costs**	**QALYSs**	**Versus DMARDs**	**Incremental**
1	DMARDs	£36,521	3.510				
8	TOC+MTX	£99,402	6.128	£62,882	2.619	£24,014	Ext Dominated
4	INF+MTX	£103,092	6.680	£66,571	3.170	£21,000	Dominated
7	ABA+MTX	£123,455	6.735	£86,935	3.226	£26,952	Dominated
6	GOL+MTX	£101,605	6.799	£65,084	3.290	£19,784	Dominated
2	ADA+MTX	£100,495	6.914	£63,974	3.404	£18,792	Ext Dominated
5	CER+MTX	£103,093	6.974	£66,572	3.464	£19,217	Dominated
3	ETA+MTX	£103,015	7.061	£66,494	3.552	£18,721	£18,721

Figure 71: Cost Effectiveness Acceptability Curves for Analysis 2 provided by AbbVie

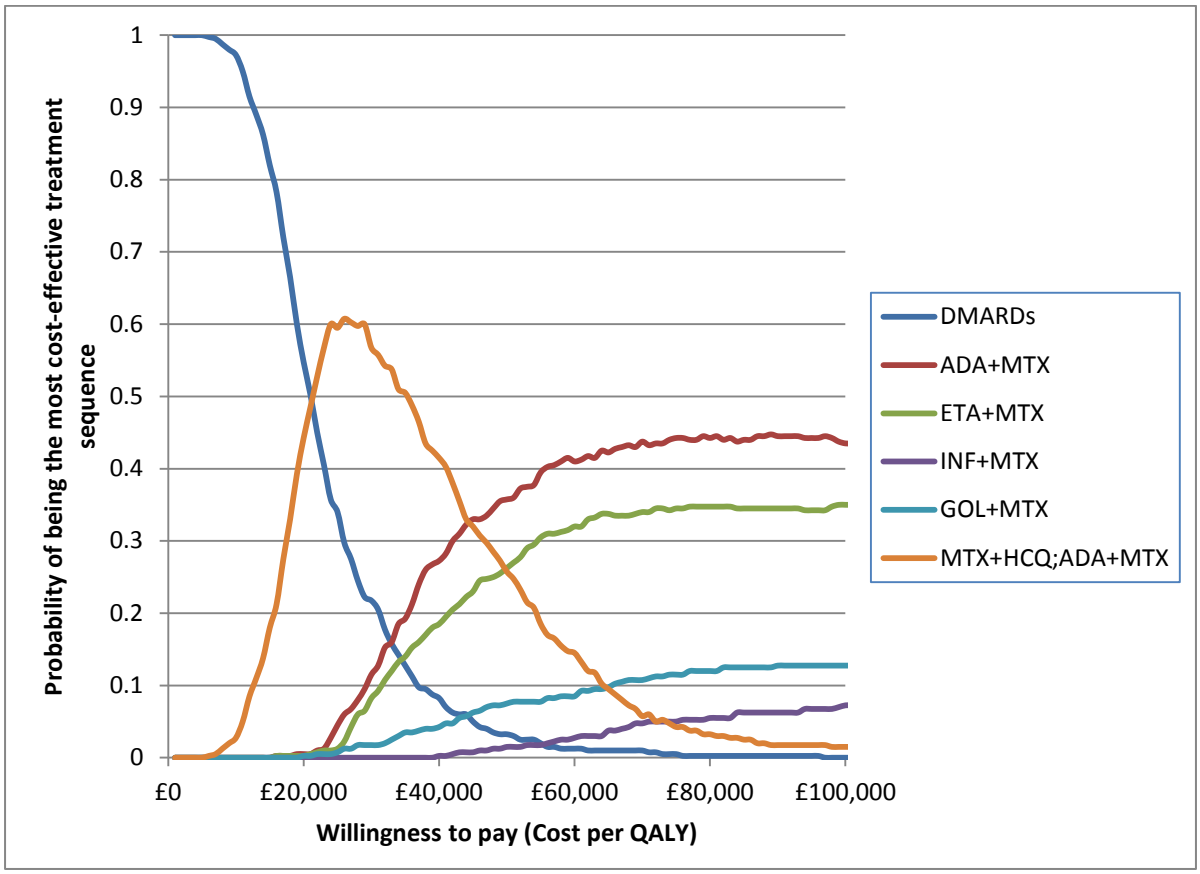


The incremental cost-effectiveness analyses for Analysis 3 are shown in Table 160 with the CEACs from the probabilistic analyses provided in Figure 72.

Table 160: Incremental cost-effectiveness ratios for Analysis 3 as reported by AbbVie

		Total		Incremental		ICER	
Sequence	**Technology**	**Costs**	**QALYs**	**Costs**	**QALYSs**	**Versus DMARDs**	**Incremental**
1	MTX	£27,076	5.104				
6	MTX+HCQ	£64,908	7.162	£37,832	2.058	£18,381	£18,381
5	GOL+MTX	£107,556	7.539	£80,479	2.436	£33,044	Dominated
3	ETA+MTX	£107,172	7.709	£80,096	2.605	£30,742	Dominated
4	INF+MTX	£113,598	7.721	£86,522	2.618	£33,055	Dominated
2	ADA+MTX	£107,097	7.765	£80,021	2.661	£30,071	£69,971

Figure 72: Cost Effectiveness Acceptability Curves for Analysis 3 provided by AbbVie



The incremental cost-effectiveness analyses are shown in Table 161 for Analysis 4 and Table 162 for Analysis 5. CEACs from the probabilistic analyses are provided in Figure 73 for Analyses 4 and Figure 74 for Analyses 5.

Table 161: Incremental cost-effectiveness ratios for Analysis 4 as reported by AbbVie

		Total		Incremental		ICER	
Sequence	**Technology**	**Costs**	**QALYs**	**Costs**	**QALYSs**	**Versus DMARDs**	**Incremental**
1	DMARDs	£29,905	2.686				
2	ADA	£51,019	3.278	£21,114	0.592	£35,641	Ext Dominated
5	TOC	£75,098	3.573	£45,193	0.887	£50,972	Dominated
4	CER	£57,245	3.579	£27,341	0.893	£30,609	Dominated
3	ETA	£56,556	3.594	£26,651	0.908	£29,338	£29,338

Figure 73: Cost Effectiveness Acceptability Curves for Analysis 4 provided by AbbVie

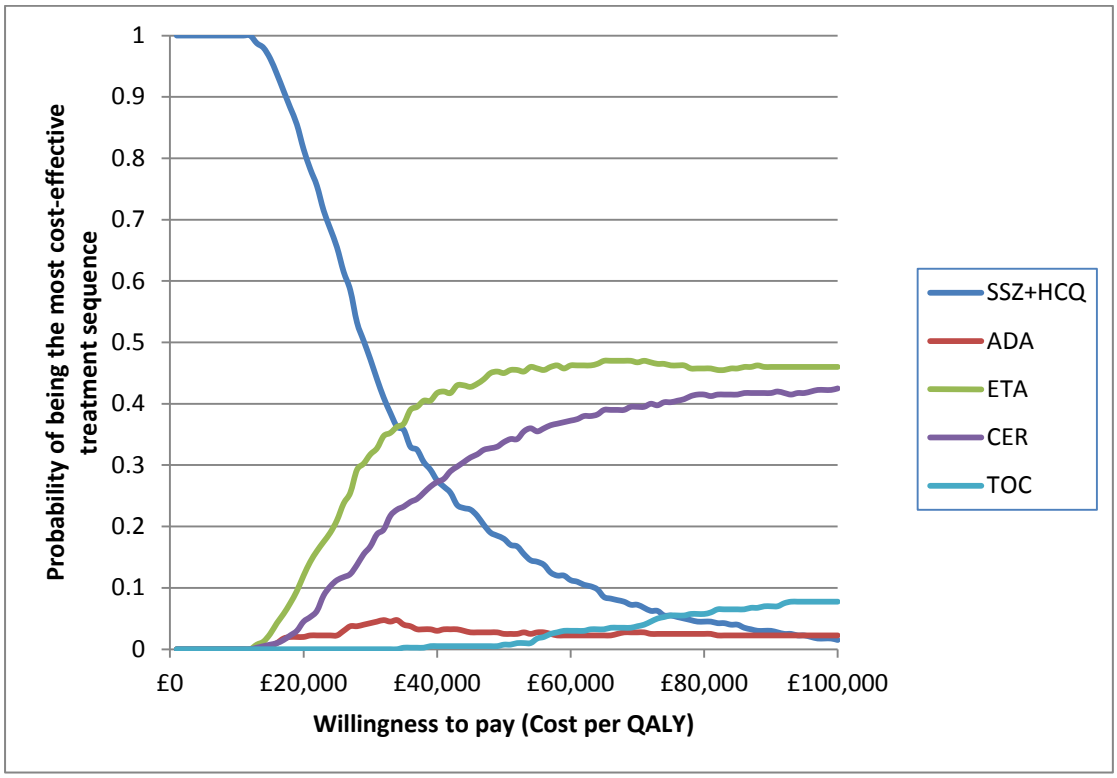
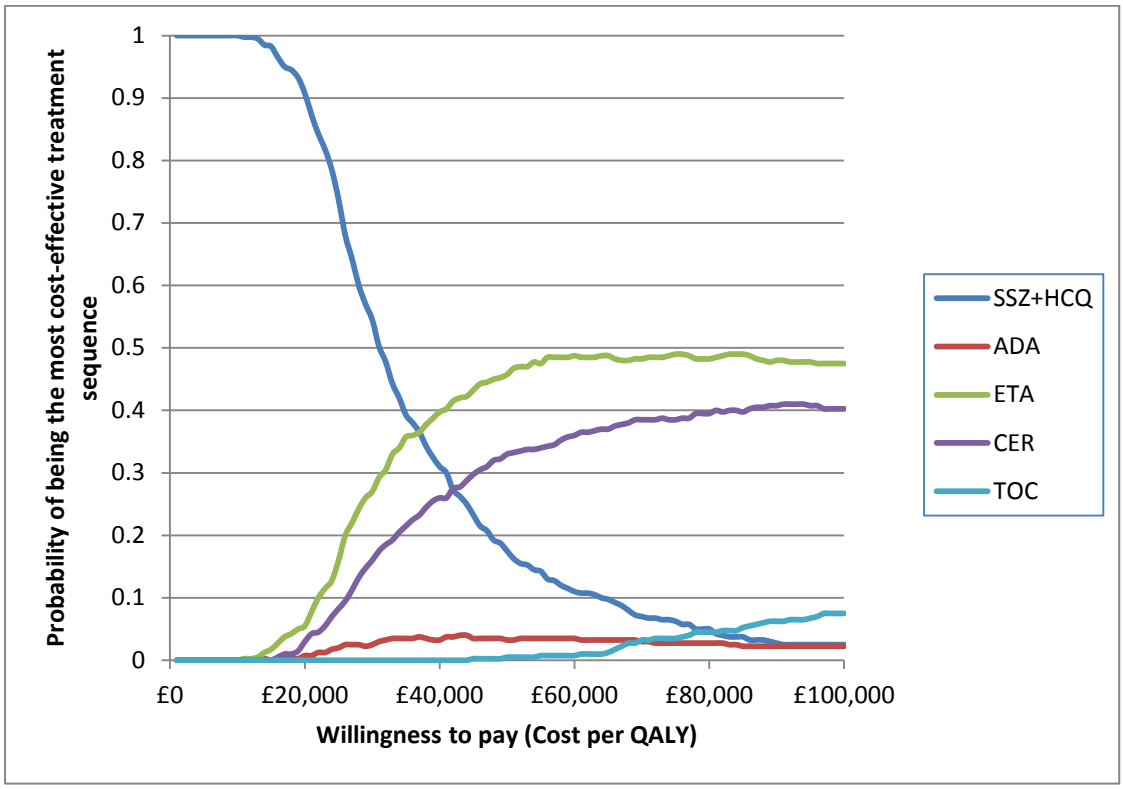


Table 162: Incremental cost-effectiveness ratios for Analysis 5 as reported by AbbVie

		Total		Incremental		ICER	
Sequence	**Technology**	**Costs**	**QALYs**	**Costs**	**QALYSs**	**Versus DMARDs**	**Incremental**
1	DMARDs	£30,113	4.319				
2	ADA	£53,107	4.907	£22,994	0.588	£39,083	Ext Dominated
5	TOC	£79,158	5.197	£49,045	0.878	£55,844	Dominated
4	CER	£59,905	5.200	£29,792	0.882	£33,791	Dominated
3	ETA	£59,272	5.222	£29,159	0.903	£32,276	£32,276

Figure 74: Cost Effectiveness Acceptability Curves for Analysis 5 provided by AbbVie

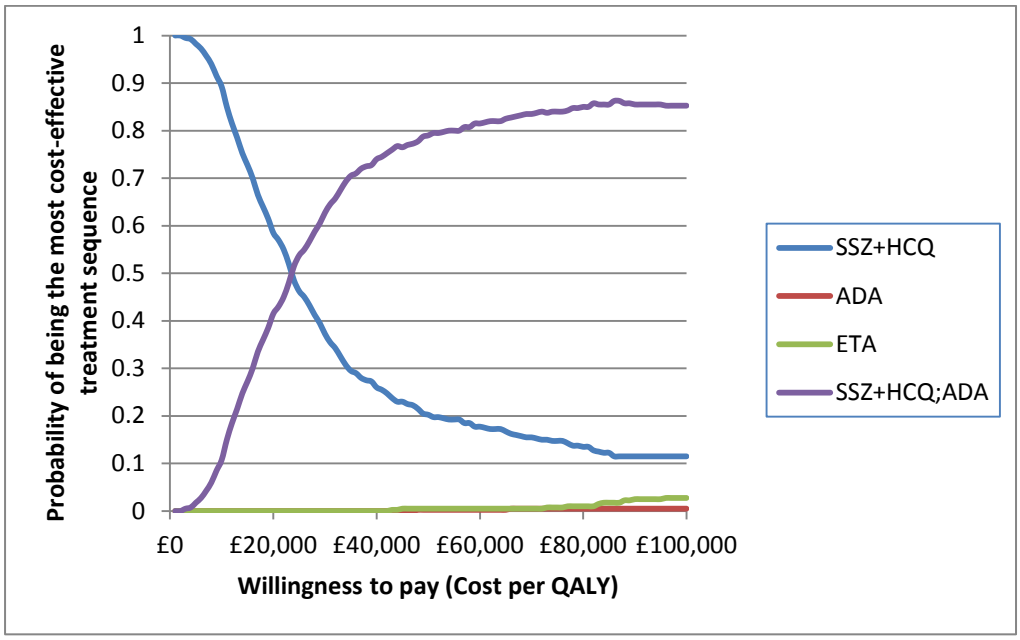


The incremental cost-effectiveness analyses for Analysis 6 are shown in Table 163 with the CEACs from the probabilistic analyses provided in Figure 75.

Table 163: Incremental cost-effectiveness ratios for Analysis 6 as reported by AbbVie

		Total		Incremental		ICER	
Sequence	**Technology**	**Costs**	**QALYs**	**Costs**	**QALYSs**	**Versus DMARDs**	**Incremental**
1	DMARDs	£29,629	5.122				
2	ADA	£60,778	5.156	£31,149	0.034	£918,015	Dominated
3	ETA	£63,859	5.293	£34,230	0.170	£201,097	Dominated
4	SSZ+HCQ (followed by ADA)	£41,703	5.774	£12,074	0.651	£18,540	£18,540

Figure 75: Cost Effectiveness Acceptability Curves for Analysis 6 provided by AbbVie



AbbVie's interpretation of their cost-effectiveness results

AbbVie state that "the main results from the cost-utility model are:

- In the MTX-experienced patient population with severe disease activity (DAS28 > 5.1), adalimumab in combination with MTX is considered cost-effective, with a lifetime incremental cost per quality-adjusted life year (QALY) gained with respect to conventional DMARDs of £16,650. This is very similar to the estimated cost per QALY of etanercept (£16,571) and certolizumab (£17,071), both taken in combination with MTX.

- In the MTX-experienced patient population with moderate disease activity (3.2 < DAS28 ≤ 5.1), adalimumab in combination with MTX is considered cost-effective, with a lifetime incremental cost per quality-adjusted life year (QALY) gained with respect to conventional DMARDs of £18,792. This is very similar to the estimated cost per QALY of etanercept (£18,721) certolizumab (£19,217) and golimumab (£19,784), all taken in combination with MTX."

Addvie conclude that their "submission demonstrates that adalimumab in combination with MTX represents a clinical and cost-effective option for the treatment of RA patients with moderate and severe disease activity, for the NHS in the UK."

It is apparent that AbbVie therefore implicitly believe that adalimumab does not represent a cost-effective first-line treatment in those patients who are MTX naïve nor when used as a monotherapy.

6.2.20.2 BMS

The submission by BMS only evaluated the use of bDMARDs in combination with MTX. The submission did not distinguish between patients with severe and moderate to severe RA, but evaluated these groups together. This did not meet the requirements of the scope and have been denoted as Analysis 7.

BMS present the disaggregated incremental costs and QALYs for the deterministic scenario, but not for the probabilistic values where only the ICER (and confidence interval around the ICER is provided. The Assessment Group note that the ICERs are lower for the probabilistic analyses than for the deterministic analyses.

The probabilistic ICERs detailed by BMS are shown in Table 164. These data are marked commercial-in-confidence. Figure 76 shows the CEAC generated by BMS

Table 164: The probabilistic ICERs for Analysis 7 provided by BMS

	ICER v DMARDs		
	Mean	95% CI Lower Bound	95% CI Upper Bound
IV abatacept	[redacted]	[redacted]	[redacted]
SC abatacept	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Tocilizumab	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]	[redacted]

DMARDs: disease-modifying anti-rheumatic drugs; ICER; incremental cost-effectiveness ratio; IV: intravenous; QALYs: quality-adjusted life years; SC: subcutaneous.

[redacted]

BMS's interpretation of their cost-effectiveness results

BMS conclude that "the results demonstrate that all of the biologics have similar ICERs when compared to DMARDs. The ICERs remain similar in scenario analyses (except when PASs are not considered). This, coupled with the overlap in the probabilistic sensitivity analysis demonstrates considerable uncertainty as to which treatment is the most cost-effective option."

6.2.20.3 MSD

The two submissions (one for golimumab and one for infliximab) from MSD will be detailed individually in terms of the cost-effectiveness results. 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.

The Assessment Group note that MSD makes not comment on the discrepant absolute QALY values in the submission (in the region of 8 for the golimumab submission and in the region of 6 for the infliximab report)

Golimumab

The Incremental analysis for Analysis 1 within the golimumab submission is reproduced in Table 165. Note that an additional column has been added to correctly calculate the incremental analysis. The CEAC for Analysis 1 is shown in Figure 77

The incremental analysis for Analysis 7 within the golimumab submission is reproduced in Table 166. Note that an additional column has been added to correctly calculate the incremental analysis. The CEAC for Analysis 7 is shown in Figure 77.

Infliximab

The Incremental analysis for Analysis 1 within the infliximab submission is reproduced in Table 167. Note that an additional column has been added to correctly calculate the incremental analysis. The CEAC for Analysis 1 is shown in Figure 78

The incremental analysis for Analysis 7 within the infliximab submission is reproduced in Table 168. Note that an additional column has been added to correctly calculate the incremental analysis. The CEAC for Analysis 7 is shown in Figure 77.

Table 165: Incremental Cost-Effectiveness Results (DMARD Experienced Severe RA Patient Population Subgroup) provided by MSD in the golimumab submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	MSD's Incremental analysis	Assessment Group's Incremental analysis
MTX	£56,036	6.425	-	-	-	-	-
Golimumab	£89,270	8.007	£33,234	1.582	£21,013	N/A	£21,013

Table 166: Incremental Cost-Effectiveness Results (DMARD Experienced RA Patient Population) provided by MSD in the golimumab submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	MSD's Incremental analysis	Assessment Group's Incremental analysis
MTX	£56,382	6.706	-	-	-	-	-
Infliximab	£88,326	8.207	£31,944	1.501	£21,278	£21,278	Ext Dominated
Etanercept	£91,025	8.068	£2,699	-0.139	£25,429	Dominated	Dominated
Golimumab	£92,130	8.307	£1,105	0.238	£22,331	£4,631	Ext Dominated
Adalimumab	£93,892	8.512	£1,762	0.205	£20,769	£8,589	Ext Dominated
Certolizumab	£97,469	8.890	£3,577	0.377	£18,817	£9,476	£18,817
Tocilizumab	£100,702	8.495	£3,233	-0.395	£24,774	Dominated	Dominated
Abatacept IV	£105,102	8.100	£4,400	-0.395	£34,953	Dominated	Dominated
Abatacept SC	£118,036	8.100	£12,934	0.000	£44,232	Dominated	Dominated

Table 167: Incremental Cost-Effectiveness Results (DMARD Experienced Severe RA Patient Population Subgroup) provided by MSD in the infliximab submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	MSD's Incremental analysis	Assessment Group's Incremental analysis
MTX	£58,181	4.504	-	-	-	-	-
Infliximab	£84,007	5.539	£25,827	1.034	£24,968	N/A	£24,968

Table 168: Incremental Cost-Effectiveness Results (DMARD Experienced RA Patient Population) provided by MSD in the infliximab submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	Incremental analysis	Assessment Group's Incremental analysis
MTX	£57,376	4.791			-	-	-
Infliximab	£83,887	5.845	£26,511	1.054	£25,144	£25,144	Ext Dominated
Etanercept	£84,947	5.678	£1,059	-0.167	£31,065	Dominated	Dominated
Golimumab	£87,027	5.909	£2,080	0.231	£26,512	£9,010	Ext Dominated
Adalimumab	£88,750	6.117	£1,723	0.207	£23,663	£8,305	Ext Dominated
Certolizumab	£93,696	6.519	£4,946	0.403	£21,011	£12,281	£12,281
Tocilizumab	£94,777	6.065	£1,080	-0.454	£29,339	Dominated	Dominated
Abatacept IV	£97,346	5.710	£2,570	-0.355	£43,455	Dominated	Dominated
Abatacept SC	£108,181	5.710	£10,834	0.000	£55,234	Dominated	Dominated

Figure 77: Cost-Effectiveness Acceptability Curve for Analysis 1 within the MSD golimumab submission

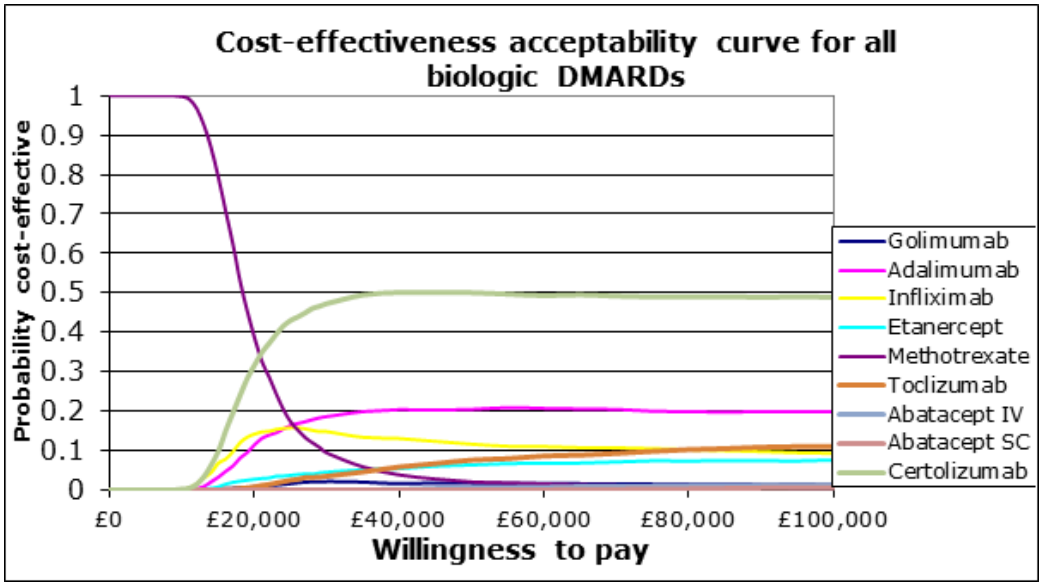
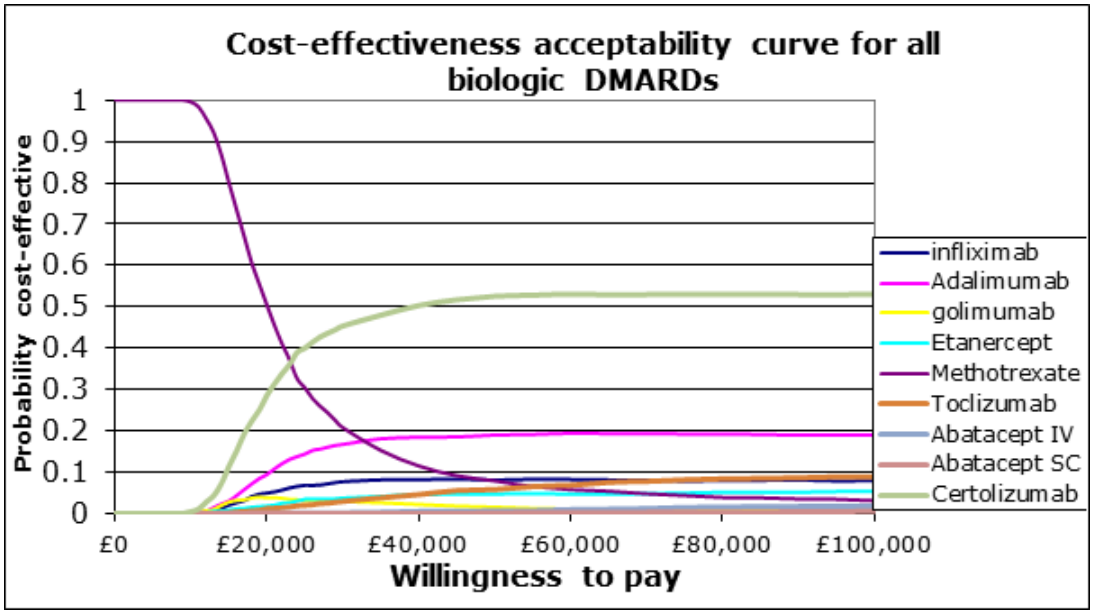


Figure 78: Cost-Effectiveness Acceptability Curve for Analysis 1 within the MSD infliximab submission



MSD's interpretation of the cost-effectiveness results in both their golimumab and infliximab submissions

MSD state "These results indicate that [drug name] is a cost-effective treatment option for patients with moderate to severe RA who have had an inadequate response to conventional DMARDs. Due to differences in trial populations and design, using ICERs to 'rank' technologies should be approached with caution and we believe that the indirect comparison results indicate a class effect as no significant differences were identified between technologies. A casing [sic] point for this would be the placebo arm dropout in the certolizumab trials which would have acted to inflate the efficacy results for this technology."

MSD additionally state that "Compared to other published studies in literature our DMARD experienced results indicate similar ICERs for TNFα inhibitors compared to palliation. Our model derives many assumptions from the BRAM and thus the ICERs are in a similar range of those approved in recent NICE appraisals.

It can be seen that the ICER for [drug name] in the severe only subgroup (DAS > 5.1) is similar to the ICER derived for the moderate-severe population and as such golimumab can be considered cost-effective in both populations and should not be limited only to the treatment of patients with severe disease."

6.2.20.4 Pfizer

Pfizer sent an addendum to the Assessment Group after detecting minor errors within their mathematical model. These errors only affected scenarios where patients were ineligible for rituximab plus MTX which are not summarised in this section.

Pfizer undertook Analyses 1 to 4. The results from these analyses are reproduced in Tables 165 to 168, with the CEACS reproduced in Figures 77 to 78.

Table 169: Severe DMARD-IR combination therapy incremental analysis presented by Pfizer

Strategy	Costs	QALYs	vs cDMARD		vs next less costly		Incremental analysis
			Inc costs	Inc QALYs	Inc costs	Inc QALYs	ICER
cDMARD	£111,612	2.638					
INF	£130,090	3.240	£18,478	0.602	£18,478	0.602	Extendedly dominated
ADA	£133,121	3.395	£21,509	0.756	£3,031	0.154	Extendedly dominated
CZP	£135,304	3.768	£23,692	1.130	£2,183	0.374	Extendedly dominated
GOL	£136,452	3.470	£24,840	0.832	£1,148	-0.298	Dominated
ETN	£140,686	4.055	£29,074	1.417	£4,233	0.585	£20,520
ABT	£151,963	3.513	£40,351	0.875	£11,277	-0.542	Dominated
TOC	£153,442	3.704	£41,830	1.066	£1,479	0.191	Dominated
ABS	£162,064	3.530	£50,452	0.891	£8,622	-0.174	Dominated

Abbreviations: ABT, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying antirheumatic drug; CZP, certolizumab; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; Inc, incremental; INF, infliximab; QALY, quality adjusted life year; TOC, tocilizumab.

Figure 79: Cost-Effectiveness Acceptability Curve for Analysis 1 within the Pfizer submission

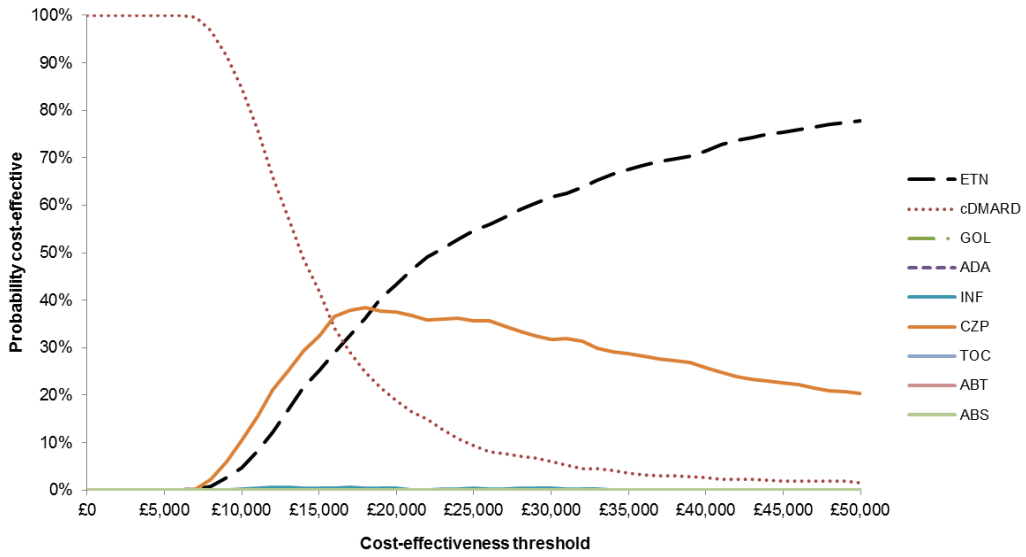


Table 170: Moderate to Severe population combination therapy incremental analysis presented by Pfizer

Strategy	Costs	QALYs	vs cDMARD		vs next less costly		Incremental analysis
			Inc costs	Inc QALYs	Inc costs	Inc QALYs	ICER
cDMARD	£128,305	8.493					
ETN	£159,730	9.764	£31,425	1.271	£31,425	1.271	£24,727

Abbreviations: cDMARD, conventional disease modifying antirheumatic drug; ETN, etanercept; ICER, incremental cost-effectiveness ratio; Inc, incremental; QALY, quality adjusted life year.

Figure 80: Cost-Effectiveness Acceptability Curve for Analysis 2 within the Pfizer submission

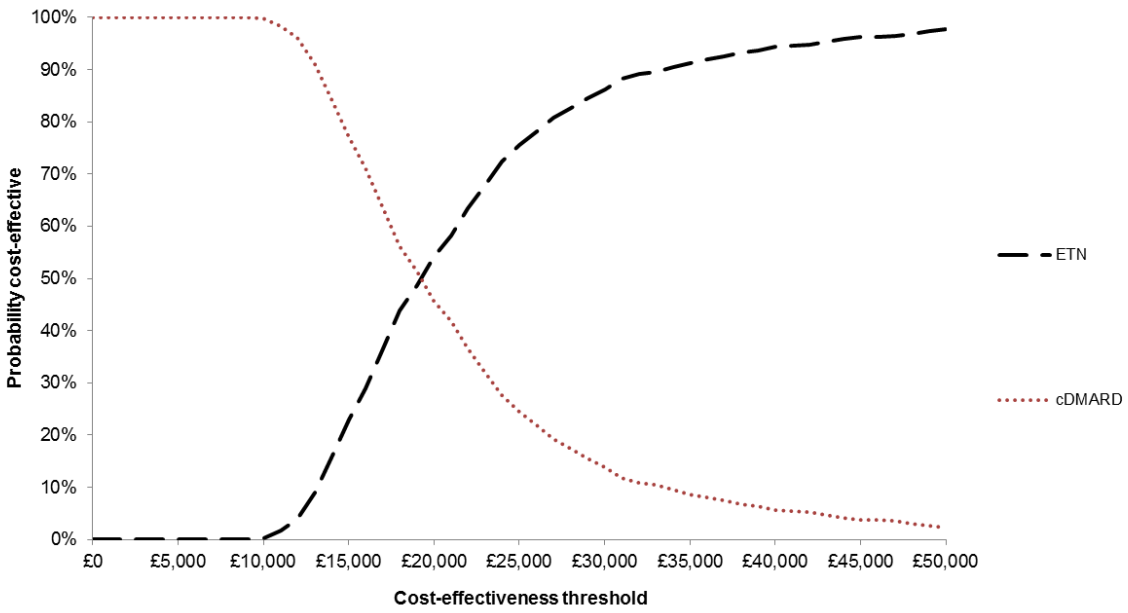


Table 171: Severe Naïve population combination therapy incremental analysis presented by Pfizer

Strategy	Costs	QALYs	vs comb cDMARD		vs next less costly		Incremental analysis
			Inc costs	Inc QALYs	Inc costs	Inc QALYs	ICER
cDMARD†	£108,488	4.754					
cDMARD	£112,462	4.615	£3,974	-0.139	£3,974	-0.139	Dominated
ETN	£150,095	5.965	£41,607	1.210	£37,633	1.350	£34,373

Abbreviations: cDMARD, conventional disease modifying antirheumatic drug; comb cDMARD, combination cDMARD; ETN, etanercept; ICER, incremental cost-effectiveness ratio; Inc, incremental; QALY, quality adjusted life year; † Combination cDMARD

Figure 81: Cost-Effectiveness Acceptability Curve for Analysis 3 within the Pfizer submission

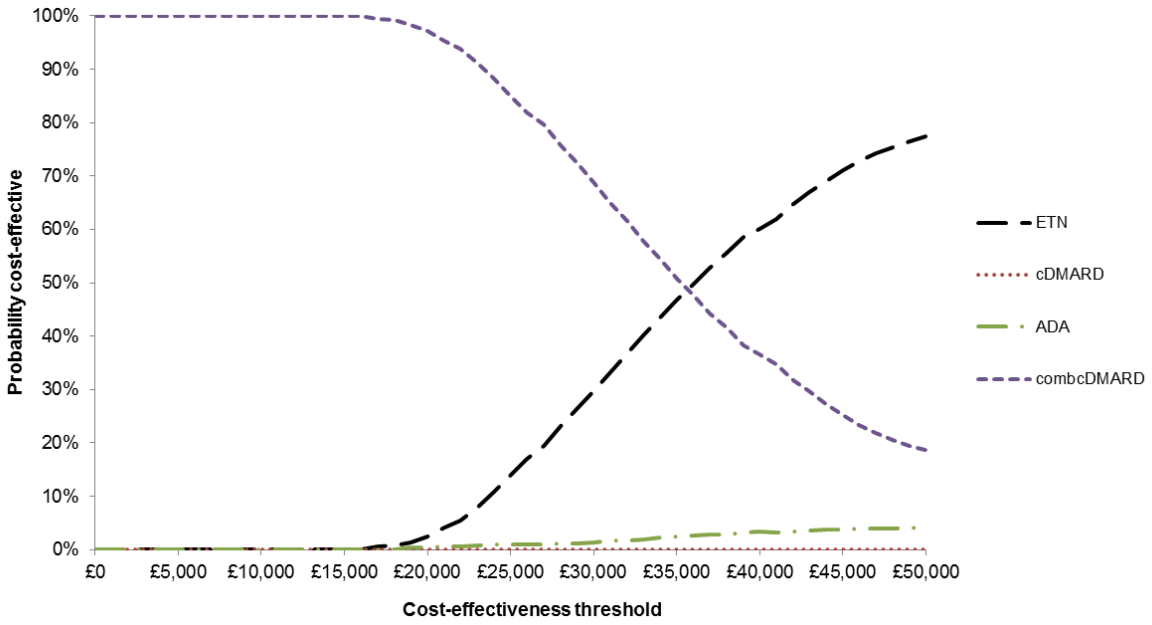
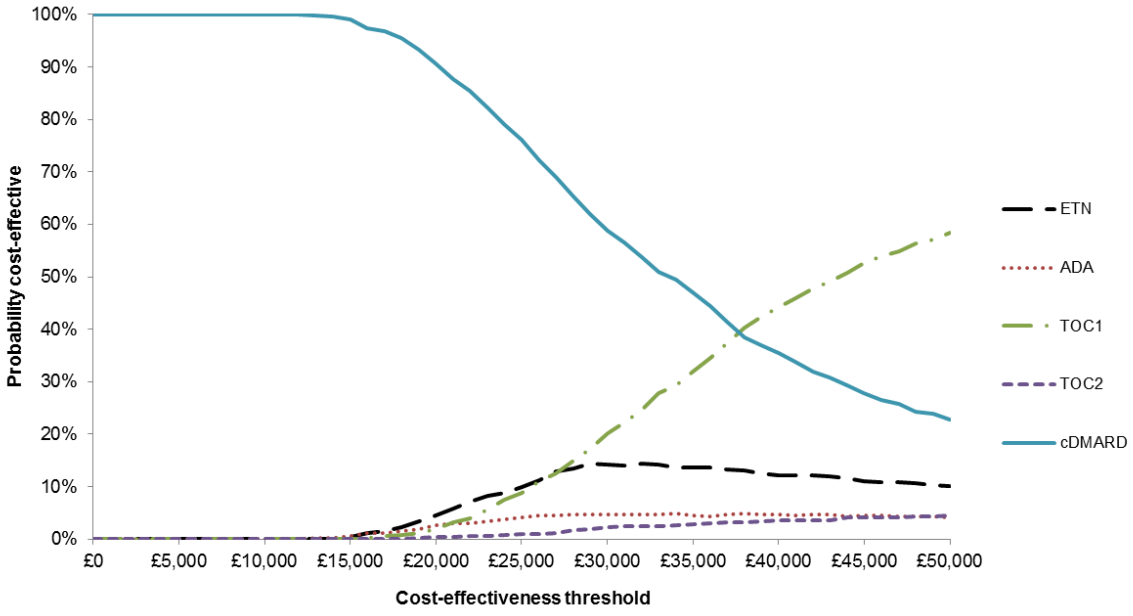


Table 172: Severe DMARD-IR monotherapy incremental analysis presented by Pfizer

Strategy	Costs	QALYs	vs ADA		vs next less costly		Incremental analysis
			Inc costs	Inc QALYs	Inc costs	Inc QALYs	ICER
cDMARD	£79,837	1.570					
ADA	£95,474	2.083	£15,637	0.513	£15,637	0.513	Dominated
ETN	£98,143	2.265	£18,306	0.695	£2,669	0.182	£26,335
TOC2	£115,782	2.642	£35,945	1.071	£17,639	0.376	Extendedly dominated
TOC1	£122,013	2.963	£42,176	1.393	£6,231	0.321	£34,227

Abbreviations: ADA, adalimumab; cDMARD, conventional disease modifying antirheumatic drug; ETN, etanercept; ICER, incremental cost-effectiveness ratio; Inc, incremental; QALY, quality adjusted life year; TOC, tocilizumab.

Figure 82: Cost-Effectiveness Acceptability Curve for Analysis 4 within the Pfizer submission



Pfizer's interpretation of their cost-effectiveness results.

Pfizer state that "the primary analysis demonstrated that, based on current NICE sequential guidance and comparisons made within the analysis, a strategy in which ETN is provided after the failure of two conventional DMARDs is the most cost-effective treatment strategy at a cost-effectiveness threshold of £30,000 per QALY in the Severe DMARD-IR combination therapy, Severe DMARD-IR monotherapy and Moderate to Severe populations. The results in a Severe-DMARD-IR population appear to be consistent with previously economic evaluations conducted from a UK perspective indentified in the economic SR, when limited or no HAQ progression has been assumed for bDMARDs.

In the Severe Naïve population, the ETN strategy had an ICER of £34,373 versus combination DMARD strategy. This result appears to be different from a previous economic evaluation conducted from a UK perspective, which suggested ETN+MTX may be cost effective at a £30,000 threshold when no HAQ progression is assumed for ETN+MTX.[113] Difference in the economic evaluations results are likely to be partially explained by difference in discount rates used, as if the alternative discount rates used in Chen et al, 2006[113] are implemented, then ETN+MTX does becomes a cost effective strategy at £30,000."

Pfizer report that the secondary analyses which were not shown in this summary that used strategies with alternative 2nd line therapies and additional comparator strategies were "unable to change the conclusions of the primary analyses. The exception was the inclusion of an alternative 2nd line therapy in the Severe DMARD-IR combination therapy population; in this analysis ETN became the optimal strategy at a cost-effectiveness threshold of £20,000 per QALY".

6.2.20.5Roche

The Roche submission evaluated a sub-population not defined in the scope as an MTX intolerant or contraindicated RA population, which was in essence Analyses 4 and 5 analysed jointly. This was denoted Analysis 8.

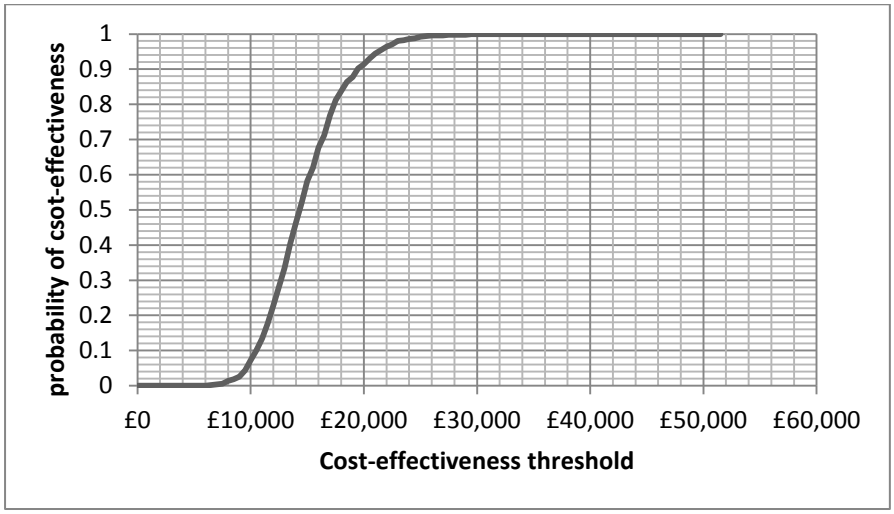
Roche's base case evaluated only adding tocilizumab as the first-line treatment to an existing sequence. The Assessment Group comment that the existing sequence is not recommended by NICE as three bDMARDs were assumed, and also that sequences of treatment should have been evaluated. For these reasons the results presented by Roche should be treated with caution.

The probabilistic results are shown in Table 173. The CEAC in Figure 82

Table 173: The probabilistic sensitivity results supplied by Roche for Analysis 8

	Standard of Care	TCZ strategy	Incremental Results	ICER (£per QALY)
Total QALYs	8.477	9.328	0.8503	
Total Cost	£123,390	£135,736	£12,346	£14,520

Figure 83: The CEAC produced by Roche for Analysis 8



Roche's interpretation of their cost-effectiveness evidence

Roche state that "the cost-effectiveness analysis results suggest that the use of first line tocilizumab for DMARD-IR rheumatoid arthritis patients who are intolerant or unsuited to MTX represents a cost-effective use of resources within the NHS. Overall, the results are robust to changes in cost and clinical parameters within the economic model, and moreover the ICERs remain cost-effective across a range of alternative methods of comparison (comparing sequences, comparing individual biologics with one another, comparing biologics to palliation alone)."

6.2.20.6UCB

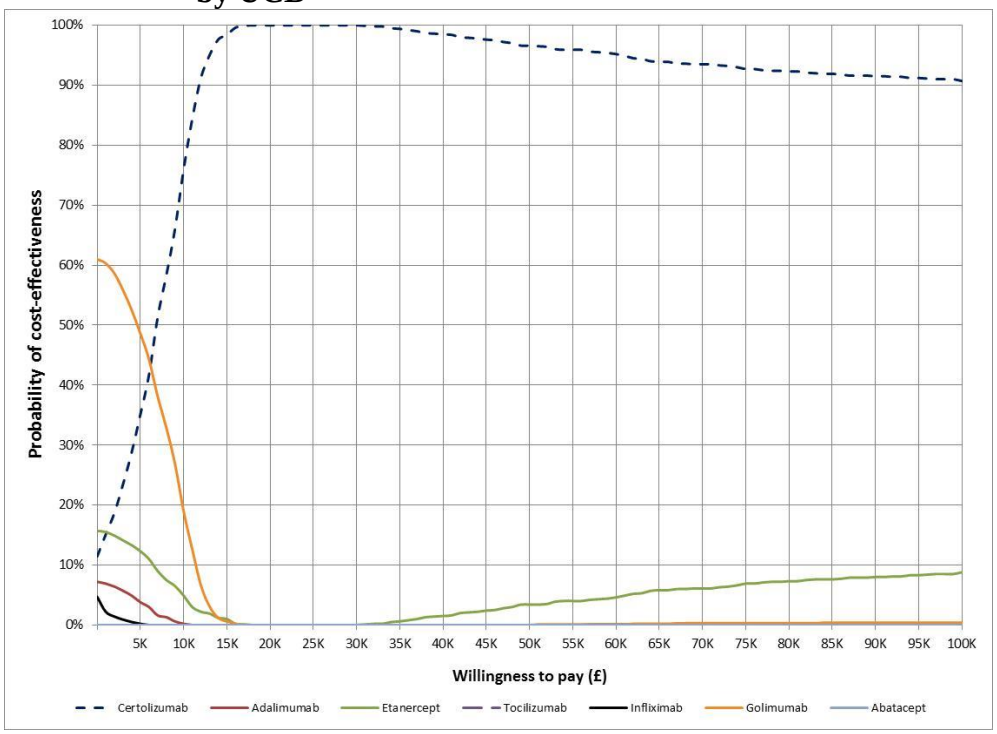
UCB presented analyses for the populations in the scope for which certeolizimub pegol was licensed. These are Analyses 1, 2, 4 and 5. The Assessment Group comment that this analyses omits a fundamental comparison which is that of bDMARD vs cDMARDS. It is unclear whether the model submitted by UCB would estimate whether bDMARDs are cost-effective given that the remaining submissions comment that the ICER for population 2 is generally similar to that for population 3, and that UCB estimate that certolizumab is not cost-effective in population 3.

The basecase results for Analysis 1 is given in Table 174, with the CEAC reproduced in Figure 83.

Table 174: Base case results for combination treatments (severe disease activity population) provided by UCB

Therapy	Mean costs	Difference in costs (CZP vs. treatment)	Mean QALYs	Difference in QALYs (CZP vs. treatment)	ICER (CZP vs. treatment)	Incremental values	Probability of cost-effectiveness at WTP of £20,000/QALY (%)
Combination therapies							
Golimumab + MTX	£126,900	£929	7.092	0.193	£4,822	Optimal at WTP threshold <£4,822	0%
Certolizumab pegol + MTX	£127,829	-	7.284	-	-	Optimal at WTP threshold >£4,822	100%
Adalimumab + MTX	£128,267	-£437	7.175	0.109	Certolizumab pegol dominates	Certolizumab pegol dominates	0%
Infliximab + MTX	£128,542	-£713	7.024	0.260	Certolizumab pegol dominates	Certolizumab pegol dominates	0%
Etanercept + MTX	£128,623	-£793	7.184	0.100	Certolizumab pegol dominates	Certolizumab pegol dominates	0%
Tocilizumab + MTX	£139,532	-£11,703	7.106	0.179	Certolizumab pegol dominates	Certolizumab pegol dominates	0%
Abatacept + MTX	£143,982	-£16,152	7.008	0.276	Certolizumab pegol dominates	Certolizumab pegol dominates	0%

Figure 84: Base case cost-effectiveness acceptability curve for Analysis 1 produced by UCB



The results for Analyses 2 and 5 were combined in Table 175. No CEACs for these analyses were provided.

Table 175: Base case results for combination treatments (moderate disease activity population) provided by UCB

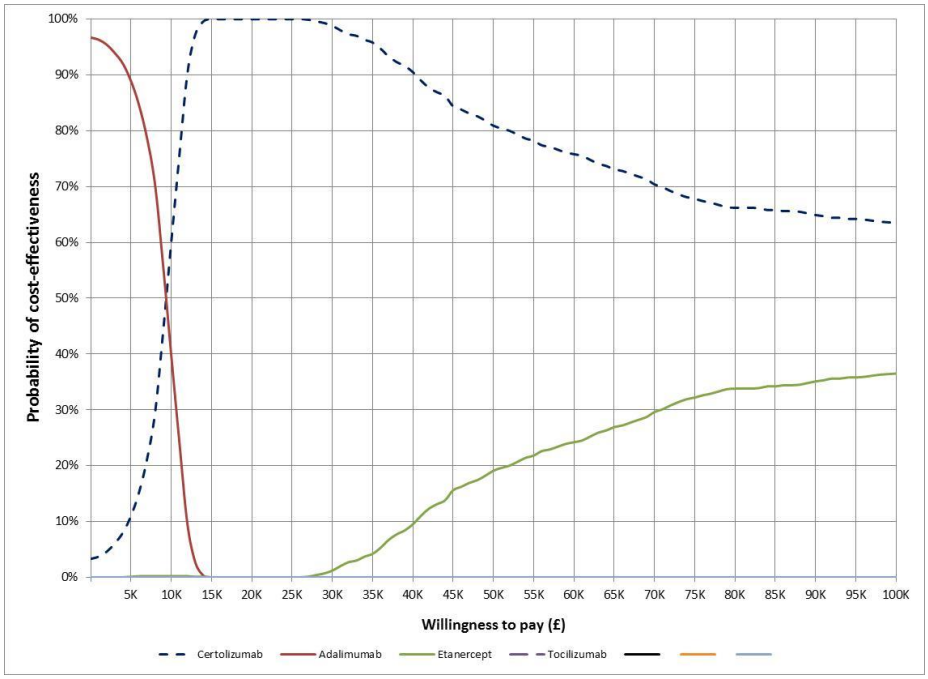
Therapy	Mean costs	Difference in costs (CZP vs. placebo)	Mean QALYs	Difference in QALYs (CZP vs. placebo)	ICER (CZP vs. placebo)	Probability of cost-effectiveness at WTP of £20,000/QALY
Combination cDMARDs therapies: Analysis 2						
CZP + cDMARD	£120,217	£29,976	9.387	0.627	£47,821	0%
Placebo + cDMARD	£90,241	-	8.760	-	-	100%
Combination MTX therapies: Analysis 5						
CZP + MTX	£116,603	£26,802	9.270	0.544	£49,226	0%
Placebo + MTX	£89,801	-	8.726	-	-	100%

UCB's base case results for Analysis 4 are provided in Table 176, with the CEAC shown in Figure 84.

Table 176: Base case results for monotherapy treatments (severe disease activity population) provided by UCB

Therapy	Mean costs	Difference in costs (CZP vs. treatment)	Mean QALYs	Difference in QALYs (CZP vs. treatment)	ICER (CZP vs. treatment)	Incremental values	Probability of cost-effectiveness at WTP of £20,000/QALY
Monotherapies							
Adalimumab	£121,595	£3,019	6.846	0.315	£9,587	Optimal at WTP threshold <£9,587	0%
Certolizumab pegol	£124,614	-	7.161	-	-	Optimal at WTP threshold >£9,587 and <£962,778	100%
Etanercept	£127,185	-£2,571	7.163	-0.003	£962,778 ETN vs. CZP	Optimal at WTP threshold >£962,778	0%
Tocilizumab	£138,971	-£14,357	7.086	0.075	Certolizumab pegol dominates	Extended dominance by certolizumab pegol and adalimumab	0%

Figure 85: Base case cost-effectiveness acceptability curve for Analysis 4 produced by UCB



UCB's Interpretation of their cost-effectiveness evidence

UCB state that "the base case analysis of the severe disease activity population indicated that certolizumab pegol has the highest probability of being cost-effective of all the combination therapies and monotherapies considered, at all willingness-to-pay thresholds between £10,000 and £100,000 per QALY. At £20,000 per QALY, CZP in combination with MTX or as monotherapy is the most cost-effective treatment with a probability of 100%."

6.2.21 Budget Impact

This section details the budget impact analyses undertaken by the manufacturers. No comment will be made on the BMS, MSD or Roche submissions as these did not include budget impacts analyses. For brevity, only summary figures for the base case will be provided rather than the methods used in the calculations. In summary, each submission that the expenditure on RA interventions would likely increase due to the increased population that would be eligible if a positive recommendation was issued for the moderate to severe RA population

6.2.21.1AbbVie

Table 177 reproduces the budget impact estimated by AbbVie assuming adalimumab was used for all eligble patients. The initial year is inflated due to treating all incident cases.

Table 177: The incremental budget impact for adalimumab when used for eligible RA patients with moderate and severe disease activity over the next 5 years in England and Wales as estimated by AbbVie

	2013	2014	2015	2016	2017
Incremental annual budget impact for RA patients with moderate and severe disease activity	£258,556,867	£149,487,523	£153,870,726	£158,282,136	£162,723,747

6.2.21.2 Pfizer

Pfizer's summarised results of the number of patients requiring treatment each year is reproduced in Table 178.

Table 178: The Number of patients requiring treatment each year as estimated by Pfizer

	2014	2015	2016
Prevalence	58,050	58,526	58,993
Incidence	1,714	1,729	1,742
Total	59,764	60,254†	60,735

Abbreviations:†rounded

6.2.21.3 UCB

UCB state that "It was estimated that the current use of the recommended biological therapy for the severe disease activity population would result in a budget impact of £225 million in 2013, rising to £234 million in 2017. A sensitivity analysis assuming an increased CZP use compared to the base case led to budgetary savings of £2.6 million over 5 years."

6.3 Independent economic assessment

Description of the Assessment Group's model

None of the models submitted by the manufacturers replicated the clinical reality within England and Wales to the satisfaction of the Assessment Group. Primarily this is because the majority of models assumed that the efficacy of the intervention was based on improvements in ACR, whereas NICE guidance has defined stopping rules where an intervention is stopped unless a DAS28 reduction of 1.2 points[27] is achieved. The criterion of achieving a 1.2 point reduction in DAS is associated with a good or moderate EULAR response.

Furthermore clinicians in the UK predominantly measure EULAR, rather than ACR responses; the use of EULAR is recommended by the BSR and British Health Professionals in Rheumatology

(BHPR), who consider the EULAR response to be an evidence-based and validated measure of response to treatment.[269]

For these reasons the Assessment Group constructed a model where the assessment of treatment response was based upon EULAR response at six months. This also alleviates the need for assumptions to be made by decision makers regarding the proportion of patients who remain on treatment following each category of ACR response.

Two of the submissions, those by BMS[265] and UCB[209], did attempt to model reductions in DAS28, however neither was considered fully appropriate. The model by BMS did not assess all of the questions within the decision problem, had minimal information on the MTC performed and additionally was written in Simul8 (a discrete event simulation software which is not included in the list of current NICE recommended packages and thus this platform could not be used by the AG). The model by UCB was a Markov cohort model that treated all patients as homogenous and would not have the flexibility desired for employing patient level covariates to represent the heterogeneity of patient outcomes.

The description of the Assessment Group's model is conducted using the same heading as employed when describing the manufacturers' models, bar the cost-effectiveness results and cost implications headings that form separate sections of this report. Where appropriate reasons why the Assessment Group has taken a different approach to the manufacturers will be provided.

The Assessment Group was granted access to data provided by the BSRBR and also from the Early Rhuematoid Arthritis Study (ERAS) and the United States National Data Bank for Rheumatic Diseases (NDB) which were used to assess key model parameters and correlations. Specific systematic reviews were undertaken for specific parameters and when these produced relevant information the papers identified are discussed. Contact was also made with key researchers in the field to identify pertinent and / or ongoing research with preliminary findings in the public domain.

6.3.1 The decision problem addressed

The Assessment Group has undertaken evaluations of all the sub-populations defined in the scope which equate to the defined Analyses 1 to Analyses 6. The Assessment Group deviated from the scope for Population 1: this was deemed necessary as the defined populations were not exhaustive and did not specify into which population a patient who had received c-DMARDs but not MTX would fall. On clinical advice such patients were assumed to be MTX naïve. The decision problem addressed

by the Assessment Group matches that undertaken by AbbVie and UCB (for the populations where certolizumab pegol is licensed.

6.3.2 The strategies modelled

This Assessment Group model considers strategies of sequencing treatments but acknowledges that due to the scope NICE can only make recommendations on the first-line use of bDMARDs. Therefore this report will assume that NICE guidance after the first biologic treatment is routinely followed. This means that rituximab with MTX will be used after failure of the first bDMARD should a patient be able to take MTX and following this a patient receives tocilizumab and MTX if not previously received.

For simplicity, it was assumed that it would be known whether a patient required monotherapy at the time of the first bDMARD initiation based on their experience to cDMARDs and also that any patient who could tolerate MTX could also receive rituximab. This would not be correct when analysing Population 1, adults with severe active RA not previously treated with cDMARDs, but is likely to be of limited impact as: (i) it would only be apparent if bDMARDs were recommended in advance of intensive cDMARDs, and (ii) the effect would be dampened as each treatment sequence would have to replace rituximab with a bDMARD that is licenced for use in monotherapy and any impact would be relatively equal across all strategies.

Although the Assessment Group model can incorporate sequences of up to seven treatments, for simplicity it was decided that modelling large number of cDMARDs would not be overly informative. The rationale for this is that there is insufficient data on the effectiveness of cDMARDs after either bDMARDs or multiple cDMARDs. For this reason, once a patient had received intensive cDMARD therapy and / or the allotted bDMARDs within the sequence, patients were assumed to have one further cDMARD (typically MTX, but an alternative cDMARD if MTX was not suitable) before moving to ‘non-biologic therapy’, which was a term defined to encompass a selection of treatments that clinicians may feel was appropriate for individual patients. It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response.

This description is in line with the data on HAQ progression that was presented by Norton et al.[270,271] Given that this assumption applies to all strategies the contraction of a cDMARD sequence to non-biologic therapy is unlikely to influence the results and should allow an easier interpretation of the results.

For populations 2 and 3, it was assumed that all patients would have previously received intensive cDMARD therapy prior to the first bDMARD and thus this intervention was not explicitly modelled.

It is acknowledged that these represent simplified pathways and that for individuals there may be alternative strategies, but the Assessment Group and their clinical advisors feel that these are fairly representative and these are also relatively in line with the typical strategies presented by the manufacturers.

Table 179 provides the broad strategies that were deemed appropriate by the Assessment Group for consideration in patients who could receive MTX.

Table 179: Broad strategies considered possible for patients who could receive MTX

	Strategy
Population 1	MTX → intensive cDMARDs → non-biologic therapy
	MTX → intensive cDMARDs → bDMARD† + MTX → rituximab + MTX→ tocilizumab+MTX → MTX→ non-biologic therapy
	MTX → intensive cDMARDs → tocilizumab + MTX → rituximab + MTX→ MTX→ non-biologic therapy
	bDMARD$^{\Delta}$ + MTX → rituximab + MTX → tocilizumab+MTX → MTX → Intensive cDMARDs → non-biologic therapy
Population 2 and 3	MTX → non-biologic therapy
	bDMARD† + MTX → rituximab + MTX→ tocilizumab → MTX → non-biologic therapy
	tocilizumab → rituximab + MTX → MTX → non-biologic therapy

cDMARDs = conventional disease-modifying anti-rheumatic drugs; bDMARDs = biological disease-modifying anti-rheumatic drugs; MTX = MTX

$^{\Delta}$ excluding abatacept, certolizumab and tocilizumab

† excluding tocilizumab

Table 180 provides the broad strategies that were deemed appropriate by the Assessment Group for consideration in patients who could not receive MTX.

Table 180: Broad strategies considered possible for patients who could not receive MTX

	Strategy
Population 1	Intensive cDMARDs → cDMARD → non-biologic therapy
	Intensive cDMARDs → bDMARD → bDMARD† → cDMARD → non-biologic therapy
	bDMARD [Δ] → bDMARD† → Intensive cDMARDs → cDMARD → non-biologic therapy
Population 2 and 3	cDMARDs → cDMARD → non-biologic therapy
	bDMARD → bDMARD† → cDMARD → non-biologic therapy

cDMARDs = conventional disease-modifying anti-rheumatic drugs excluding MTX; bDMARDs = biological disease-modifying anti-rheumatic drugs (limited to adalimumab, certolizumab pegol, etanercept and tocilizumab); MTX = MTX

[Δ] excluding abatacept, certolizumab and tocilizumab

† excluding tocilizumab

The broad strategies were distilled into the following strategies which were evaluated (Tables 181 to 184). The Assessment Group believes that these provide representative results. These strategies are not significantly different to those of the manufacturers bar the exclusion of named cDMARDs at the end of the sequence. Given the large uncertainty in the efficacy of the cDMARDs in post-bDMARD or post-Intensive cDMARDs the inclusion of specific interventions may be introducing spurious accuracy.

Table 181: The strategies evaluated for Populations 2 and 3 for those who can receive MTX.

	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
Strategy 1	MTX	NBT			
Strategy 2	ABT iv+	RTX+	TCZ+	MTX	NBT
Strategy 3	ABT sc+	RTX+	TCZ+	MTX	NBT
Strategy 4	ADA+	RTX+	TCZ+	MTX	NBT
Strategy 5	CTZ+	RTX+	TCZ+	MTX	NBT
Strategy 6	ETN+	RTX+	TCZ+	MTX	NBT
Strategy 7	GOL+	RTX+	TCZ+	MTX	NBT
Strategy 8	IFX+	RTX+	TCZ+	MTX	NBT
Strategy 9	TCZ+	RTX+	MTX	NBT	

'+' with MTX; ABT iv - abatacept iv; ABT sc – abatacept sc; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; Gol – golimumab; IFX – infliximab; NBT – non-biologic therapy; RTX – rituximab; TCZ - tocilizumab

Table 182: The strategies evaluated for Populations 2 and 3 for those who cannot receive MTX.

	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
Strategy 1	SSZ	NBT			
Strategy 2	ADA	ETN	TCZ	SSZ	NBT
Strategy 3	ETN	ADA	TCZ	SSZ	NBT
Strategy 4	TCZ	ADA	SSZ	NBT	

ADA – adalimumab; ETN – etanercept; NBT – non-biologic therapy; SSZ – sulfasalazine; TCZ - tocilizumab

Table 183: The strategies evaluated for Population 1 for those who can receive MTX.

	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment	Sixth-line treatment	Seventh-line treatment
Strategy 1	MTX	Int CD+	MTX	NBT			
Strategy 2	MTX	Int CD+	ADA+	RTX+	TCZ+	MTX	NBT
Strategy 3	ADA+	RTX+	TCZ+	MTX	NBT		

'+' with MTX; ADA – adalimumab; NBT – non-biologic therapy; RTX – rituximab; TCZ - tocilizumab

Table 184: The strategies evaluated for Population 1 for those who cannot receive MTX.

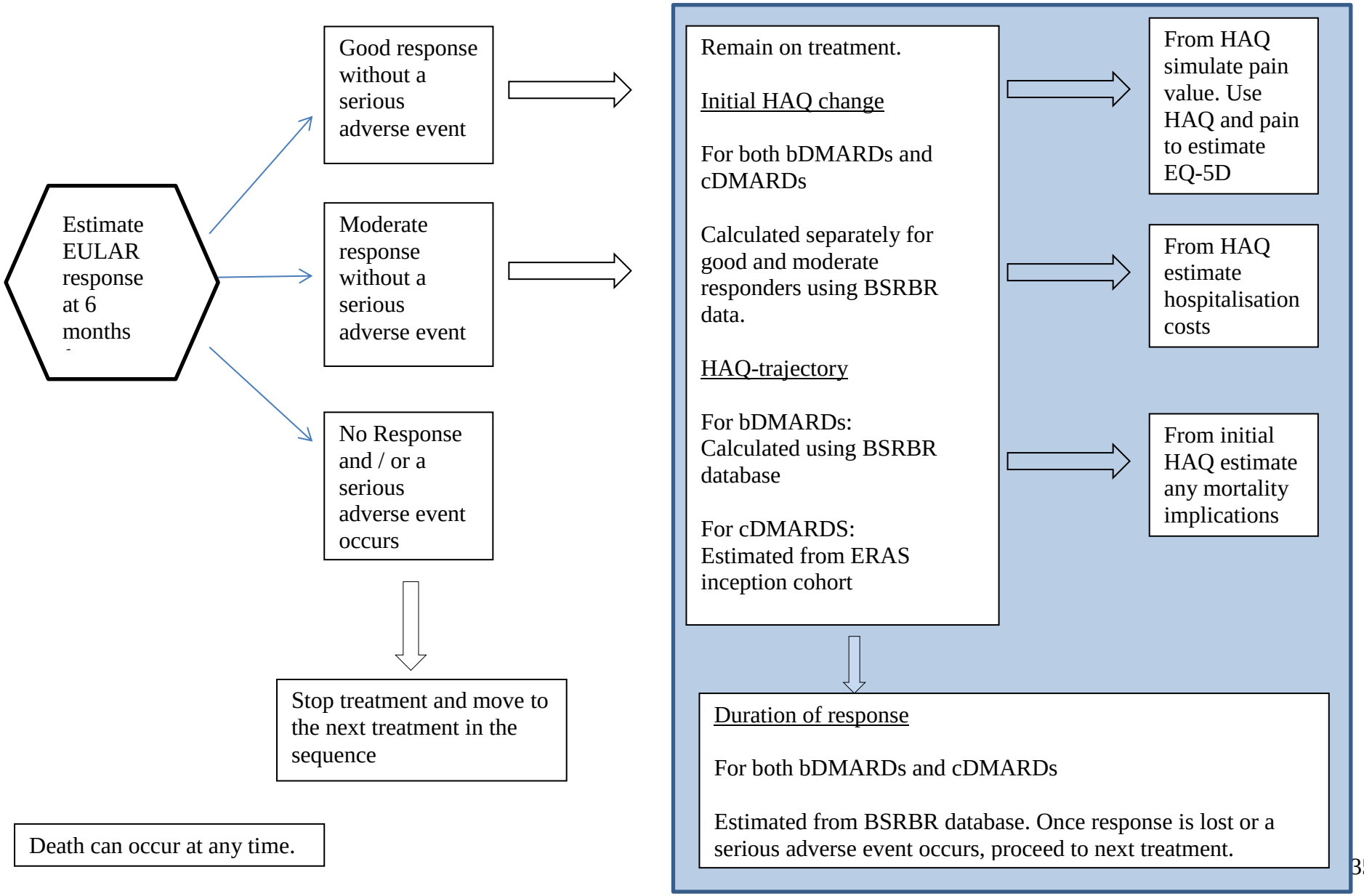
	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment	Sixth-line treatment
Strategy 1	MTX	NBT				
Strategy 2	MTX	ADA	ETN	TCZ	MTX	NBT
Strategy 3	ADA	ETN	TCZ	MTX	NBT	

'+' with MTX; ADA – adalimumab; NBT – non-biologic therapy; RTX – rituximab; TCZ - tocilizumab

6.3.4 Model Structure / Time Cycle

A simplified schematic of the Assessment Group's model is shown in Figure 86. The model is individual-patient based and uses a discrete event simulation approach. Therefore a time cycle was not employed. The model allows only legitimate HAQ scores (the 25 points defined in the 0 to 3 range) with time to a change in HAQ score being a competing risk. The advantage of using discrete HAQ scores means that if some outputs (such as costs, utility or risk of mortality) are assumed related by HAQ there is no need to be continually updating the output as a HAQ score is assumed to linearly progress between legitimate HAQ points.

Figure 86: Conceptual simplified schematic of the modelling process.



The Assessment Group model differs substantially to that of the manufacturers as it is EULAR based and uses large databases for population of key parameters such as the initial HAQ changes conditional on EULAR response, and HAQ trajectory based on EULAR response.

6.3.5 Time Horizon

The Assessment Group model employs a lifetime patient horizon but assumes that no patient will live beyond 101 years. This is similar to the approaches undertaken in the manufacturer's submission.

6.3.6 Perspective

The Assessment Group model employs a direct NHS and personal social services perspective which is in line with that adopted by the manufacturers.

6.3.7 Discounting

The Assessment Group model used discount rates of 3.5% per annum for both costs and benefits as recommended within both the 2013 NICE methods guide[272] and the 2008 methods guide.[194] A sensitivity analyses were undertaken assuming values of 6.0% for costs and 1.5% for benefits.

6.3.8 Population characteristics

The Assessment Group samples patients who are MTX-experienced from the BSRBR which allows correlation to be maintained between the following characteristics: age; gender; disease duration; DAS; previous DMARDs; HAQ and weight. Individual patients were resampled until the patient met the criteria for the population being analysed. This approach significantly increased the running times for those patients with a DAS score between 3.2 and 5.1 as these represented a minority of patients in the BSRBR and required considerable resampling.

Having sampled the patient's characteristics the HAQ score is set at a legitimate value. As an example, suppose that a non-legitimate HAQ of 1.600 was simulated. Sampling the probabilities of the bordering legitimate HAQ scores in inverse relation to their distance from

1.6 (20% chance of being 1.5 and 80% chance of being 1.625) would retain the mean value but allow legitimate HAQ scores. Thus in this example we would simulate 80% of patients having a HAQ score of 1.625 with the remaining patients having a HAQ of 1.5 rather than 100% having a HAQ of 1.600.

The Assessment Group populated patients' characteristics based on the BSRBR whereas a number of manufacturers have used the patient characteristics from their pivotal trials to populate their mathematical models. The advantage of the Assessment Group approach is that it is a much larger dataset (7250 patients), it is representative of people treated in England and Wales and the correlation structure between parameters is maintained. A disadvantage is that the dataset for moderate to severe RA patients is much smaller approximately 500 patients, although this is not small relative to the numbers of patients within the RCTs.

For patients who are MTX-naïve it was deemed that the BSRBR database was not an appropriate data source as this would contain a very small number of such patients. Both AbbVie and Pfizer presented population characteristics for MTX-naïve patients with a DAS score greater than 5.1 Of the two estimates, that of Pfizer based on the COMET trial [73] was deemed more appropriate as the disease duration was of 1 year compared with 11.28 years reported by AbbVie citing Breedveld [99]which was thought to be a long period without having experienced MTX. The estimate from Pfizer had a greater HAQ at baseline (1.70 compared with 1.38) and were on average younger (a mean age of 51.4 years compared with 60)

6.3.9 Costs of the interventions

The costs of the interventions are detailed in Table 185.

These costs are similar to those used by the manufacturers however there are two comments worth noting: i) that the Assessment Group takes all patient access schemes into consideration whereas the majority of manufacturers do not and ii) that a number of manufacturers have assumed a fixed weight per person that can underestimate the costs of weight-based interventions.

An additional treatment option is listed in Tables 183 and 184 that are not interventions within the NICE scope: rituximab plus MTX.

The costs of other drugs used within the sequence (rituximab and the costs of cDMARDs) are provided in Table 185.

Table 185: The costs of cDMARDs and rituximab

Treatment	Dose regimen	Cost per cheapest dose[1]	Cost of first 6 months [2]	Subsequent annual treatment cost [2]
Rituximab	2000mg every 9 months	£3,492.60 (2000 mg)	£3,492.60	£4,656.80[3]
Hydroxycholoroquine	6.5mg/kg per day (max. 400mg per day)	£0.17 (400mg)	£31.35 [4]	£62.70 [4]
Methotrexate	7.5mg per week escalated by 2.5mg per week up to 20mg per week	£0.80 (20mg)	£19.32	£41.57
Prednisolone	7.5mg per day	£1.07 (7.5mg)	£196.25	£392.50
Sulphasalazine	500mg per day escalated by 500mg per week up to 3000 mg per day	£0.79 (3000mg)	£131.38	£290.17
Intensive combination DMARD therapy [5]	Hydroxycholoroquine + methotrexate + prednisolone + sulfasalazine (doses as per monotherapy treatments)	NA	£378.31	£786.94
Palliative Care/Rescue Therapy	N/A [5]	Assumed £60 per month [6]	£360	£720

[1] Note that dose can be daily or weekly (see Dose regimen). [2] No administration or monitoring costs included. [3] Rituximab is administered at discrete 9 month periods. [4]Using BSRBR average weight of 73kg for illustration. [5]Intensive combination DMARD therapy is assumed to be the individual regimens for Hydroxycholoroquine, Methotrexate, Prednisolone and Sulfasalazine combined.. [6]An approximation of monthly 'post biologic' cDMARD therapy (Leflunomide, gold, cyclosporine etc.) NA = not applicable

6.3.10 Costs of administration and monitoring

The administration costs of infusions were taken from TA247[195] in which the final appraisal determination (FAD) stated that 'the manufacturer's revised estimate of £154 was acceptable'. This estimate (of 60 minutes infusion time was also applied to abatacept and infliximab) in the absence of a robust relationship between costs and infusion times. This assumption may be favourable to infliximab and unfavourable to abatacept as the recommended infusion times are at least 2 hours, and 30 minutes respectively. The FAD for TA247 did not comment on the assumption that 10% of subcutaneous injections would be performed by district nurses and the Assessment Group has assumed that these were also thought acceptable. This resulted in an average administration cost per subcutaneous injection of £2.61. Neither of administration costs has been inflated as they were relatively recent and there is uncertainty in the direction of costs in the current economic climate. The

value used by the Assessment Group is in broad agreement with the majority of manufacturers.

The assumed monitoring costs are provided in Table 186. These are assumed equal for MTX and bDMARDs.

Table 186: The monitoting costs assumed

Monitoring component	FBC[1] £2[5]	ESR[2] £3[5]	BCP[3] £3[5]	CXR[4] £33[5]	Urinalysis £0.09[6]	Hospital outpatient attendance £128[6]	Total Cost
Methotrexate monitoring – before treatment initiation	1	1	1	1	0	1	£170
Methotrexate monitoring – first 6 months of treatment	10	0	10	0	0	10	£1,700
Monthly monitoring cost	1	0	1	0	0	1	£134

[1]Full Blood Count, [2]Erythrocyte sedimentation rate, [3]Biochecmical profile, [4]Chest X-ray, [5]NHS Reference Costs 2012, [6] .Malottki et al[202]

6.3.11 Comparative treatment efficacy (Mixed Treatment Comparison)

The MTC undertaken by the Assessment Group has been detailed in Section 5.3. For information graphical depiction of the estimated proportions of EULAR response are provided in Figures 87 to 89 for EULAR and in Figures 89 to 92 for ACR mapped to EULAR. It is stressed that these figures do not reflect the considerable uncertainty in the values and reflect mean estiamtes only.

Figure 87: Estimated mean EULAR responses (main analyses)

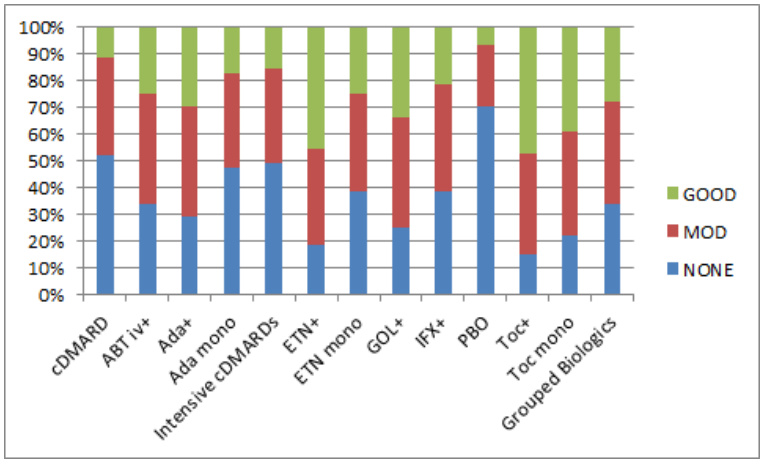


Figure 88: EULAR mean EULAR responses (main analyses plus RCTs with a small level of bDMARD use)

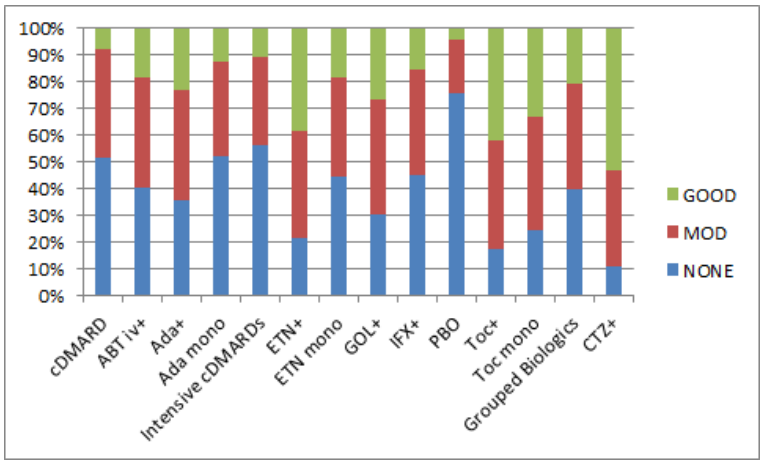
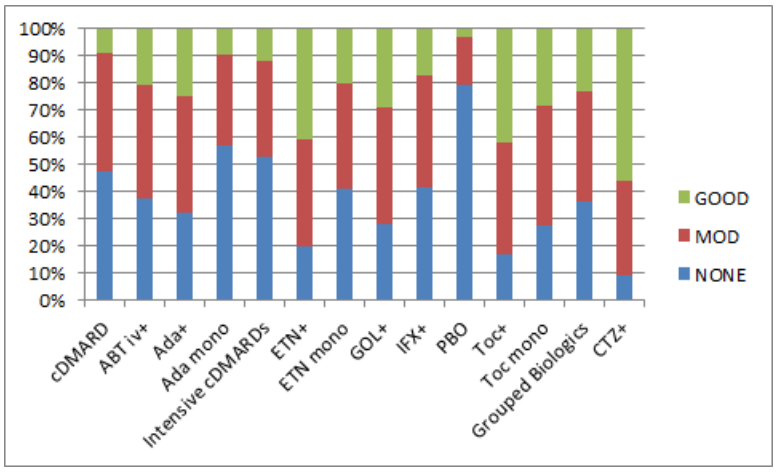


Figure 89: Estimated mean EULAR responses (main analyses plus RCTs with a small level of bDMARD use and also allowing a trial with low MTX-background use)



The Assessment Group model reflects current NICE guidance, and UK practice by simulating patient response in terms of EULAR categories (none, moderate, good). However, the evidence on clinical effectiveness does not universally report EULAR responses, with ACR categories widely used. In order to inform the evidence synthesis and to be able to make use of the entirety of the evidence base in the most informed and efficient manner, we sought evidence of the relationship between these response categories using individual patient level data.

The Veterans Affairs Rheumatoid Arthritis (VARA) registry provided such estimates to the Assessment Group as academic-in-confidence. VARA is a multi-centre, US database of veterans over the age of 19yrs. (Table 187)

Analyses were undertaken i) using both version of EULAR response (CRP based and ESR based) and ii) for all patients and just those with DA28>5.1 at baseline. These are shown in Table 187. The ESR based values were used as these was reported most regularly in the RCTs

Table 187: The relationship between EULAR responses and ACR responses in the VARA database

	Less	*ACR20*	*ACR50*	*ACR70*	*total*
EULAR ESR, all patients					
EULAR None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EULAR ESR, severe active					
EULAR None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

By assuming that the relationships shown in Table 187 were correct then it was possible to use data taken from the network meta-analysis of ACR by mapping this onto EULAR data and subsequently using the same procedures as for the Assessment Group model.

The following assumptions have been made regarding the efficacy of rituximab based on work by Malottki et al.[202] Table 46 in Malottki et al reports that in terms of ACR20, ACR50, ACR70 and withdrawal for any reason that the indirect comparison of rituximab versus abatacept either favoured rituximab, albeit with wide confidence intervals or there was no difference. Given these data the efficacy of rituximab was assumed equal to iv abatacept iv.

Figure 90: Estimated mean EULAR response mapped from ACR trials (main analyses)

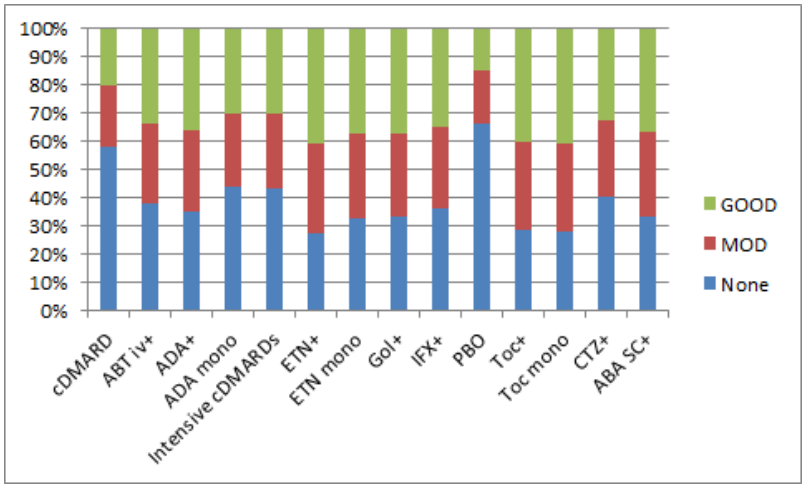


Figure 91: Estimated mean EULAR response mapped from ACR trials (main analyses plus RCTs with a small level of bDMARD use)

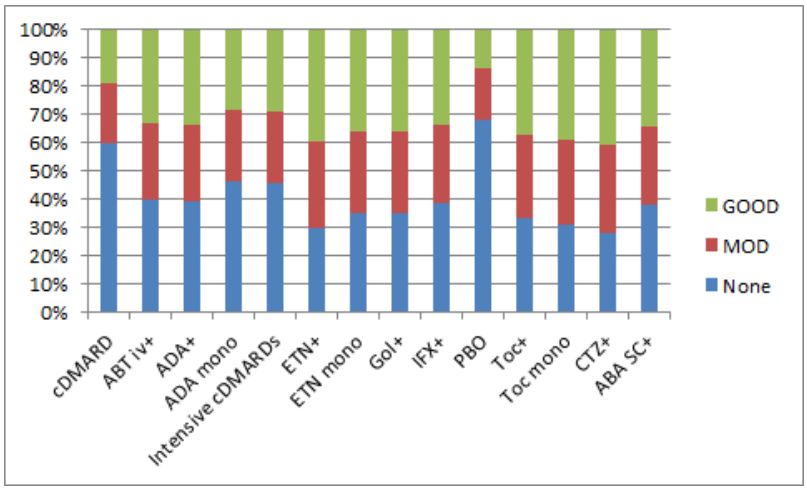


Figure 92: Estimated mean EULAR response mapped from ACR trials (main analyses plus RCTs with a small level of bDMARD use and also allowing a trial with low MTX-background use)

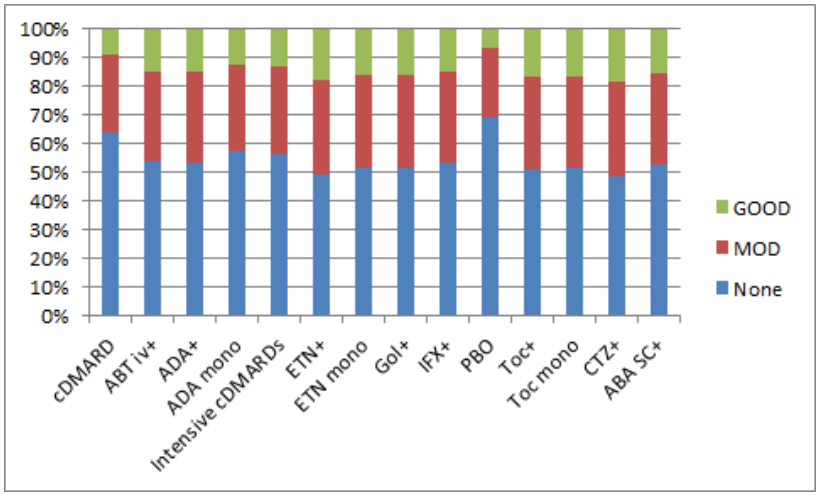
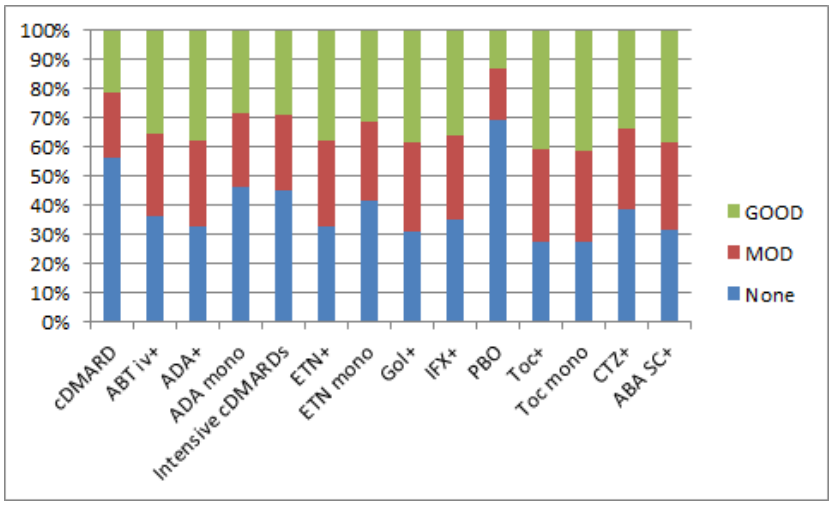


Figure 93: Estimated mean EULAR response mapped from ACR trials (main analyses plus RCTs with low MTX-background use)



There are no marked differences between the results produced by the Assessment Group and the combined evidence presented by the manufacturers.

6.3.12 Responder criteria

The Assessment Group model is based on EULAR response category (Good / Moderate / None) in order to reflect current NICE guidance on biologic therapies in RA and to align more closely to UK clinical practice in terms of the assessment of response to therapies.. The estimated probability of each EULAR response has been taken from the MTCs conducted by the Assessment Group. This allowed analyses to be conducted purely on EULAR data or estimated based on ACR responses in order to encompass a wider evidence base. This differs from the majority of submissions which assumed that ACR responses would be used to determine whether patients were responders or not i.e. there is an implicit stopping rule associated with ACR and its relationship to EULAR criteria that underpins these models, though this is not explicitly stated.

6.3.13 HAQ / EQ-5D changes in relation to response levels

This section has been divided into two subsections: one relating to bDMARDs and one relating to cDMARDs. In addition to the values assumed by the Assessment Group in our base case, sensitivity analyses were run using values associated with HAQ change conditional on EULAR response for cDMARDs,

bDMARDS

As the HAQ change and predicted HAQ trajectory for those receiving bDMARDs are closely linked within the statistical analyses undertaken within the BSRBR database, the detail of the estimation in HAQ change following EULAR response for bDMARDS has deferred until the 'HAQ trajectory following initial response' section with summary data presented here.

For patients with the mean characteristics of the actual sample of EULAR moderate responders within the BSRBR, the statistical model predicts a change of 2.08 to 1.79 (a change of 0.29). The mean change in the raw data for this group is 2.08 to 1.75 (a change of 0.33). For patients with the mean characteristics of the actual sample of EULAR good responders the statistical model predicts a change of 1.81 to 1.27 (a change of 0.54). The mean change in the raw data for this group is 1.81 to 1.26 (a change of 0.55).

The Assessment Group assume that the relationship between EULAR response and HAQ improvement is independent of bDMARD.

The statistical model that estimates HAQ change at 6 months and beyond, conditional on EULAR response category, is designed to do so at the individual patient level. However, since the ScHARR model is not a true patient level model in the sense that many of the functions in fact are programmed to estimate the average course of a patient, and because using this statistical model at the patient level substantially increased computational run time, we instead used the mean 6 month HAQ improvement for all patients. This was calculated by setting all characteristics at their mean values and assuming that the model error and mean random effect were both set to zero.

The Assessment Group assume that the relationship between EULAR response and HAQ improvement is independent of bDMARD.

The statistical model estimating initial response is calculated at the individual patient level; however as the data for cDMARDs was only at the aggregate level, aggregate data for bDMARDs was used. Without this adaptation the results would be unfavourable to bDMARDs as individual patients could be predicted to have a HAQ increase despite a Good EULAR response, and when this is combined with the non-linear mapping of HAQ to utility such patients would have a disproportionate weight when calculating the average QALYs.

cDMARDS

In the base case the Assessment Group assume that the HAQ change, conditional on EULAR response, was the same for cDMARDs as for bDMARDs. However data specifically for cDMARDs was also identified and is detailed here. The analyses assume that HAQ change, conditional on EULAR response is equal irrespective of the treatment (cDMARD or bDMARD).

The mean HAQ improvement observed for patients on cDMARDs according to their EULAR response between baseline and 6 months was calculated based upon data within the ERAS dataset. These data are shown in Table 188 for all patients between baseline and 6 months later.

Table 188: Mean HAQ improvement by EULAR response category for those on cDMARDs

	HAQ					
EULAR response baseline>6month visits						
	mean	se	z	p	lcl	ucl
None	-0.050	0.025	-2.03	0.043	-0.098	-0.002
Moderate	-0.509	0.035	-14.67	0.000	-0.577	-0.441
Good	-0.650	0.043	-15.10	0.000	-0.735	-0.566

Se = standard error

lcl = lower 95% confidence interval; ucl = lower 95% confidence interval

It is seen that the average HAQ improvement for both moderate and good EULAR responses were markedly larger than that for no EULAR response. Due to the nature of the model it was possible in some instances the HAQ improvement for those with a moderate EULAR response was greater than those with a good EULAR response.

The methods used by the Assessment Group differ from those used by the majority of the manufacturers which assume that the relationship between HAQ and ACR response observed within their key trials is applicable to all interventions. These assumptions use a relatively small sample size and may be subject to variability as observed in the two MSD submissions where the assumed HAQ changes per ACR level are markedly different. Additionally the patients recruited to RCTs may be not be representative of those patients who will treated: this could onfluence the relation between the absolute change in HAQ and HAQ at baseline.

6.3.14 HAQ trajectory following initial response

This section has been divided into two subsections: one relating to bDMARDs and one relating to cDMARDs.

In addition to the values assumed by the Assessment Group in our base case, sensitivity analyses were run using values considered within previous NICE technology appraisals. These assumed that the HAQ trajectory on biologics is flat, 0.045 per annum whilst on cDMARDs and 0.06 per annum whilst on 'palliative care' (which equated to non-biologic therapy in the Assessment Group model) the HAQ trajectory increased by 0.06 per annum.

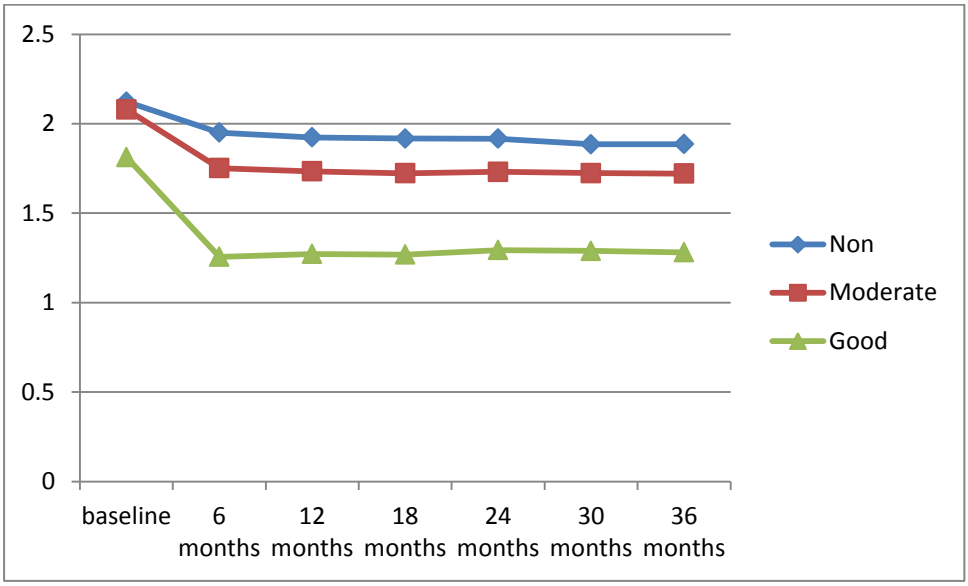
bDMARDS

In order to estimate the trajectory of HAQ the BSRBR database was used. The BSRBR database measures HAQ at 6 month intervals for all registered patients for a maximum of three years. The evolution of HAQ whilst a patient remains on a biologic therapy was estimated as a function of a patient's baseline characteristics and 6-month EULAR response category.

The patient data was restricted to those patients who had a full set of baseline characteristics including HAQ and at least two other recorded measurements of HAQ whilst on a biologic therapy. The only bDMARDs for which there were sufficient follow up time were deemed to be etanercept, infliximab and adalimumab.

There are 10,186 such patients in the dataset of which 2417 are EULAR good responders, 5492 are EULAR moderate responders and 2277 are EULAR non-responders (of whom a quarter of these had treatment longer than four years' duration). Figure 93 shows the average HAQ in the sample by EULAR response. It is seen that HAQ decreases in the first six months after starting on a biologic therapy (with the level of decrease greater as the level of EULAR response increases) and levels off towards the end of the three years' observation period. For goor responders there is a degree of loss of initial 6 month HAQ improvement in subsequent periods. It is important to note that there is imbalance between the three groups of responders. For example, it can be seen that "good" EULAR responders have a lower baseline HAQ than "moderate" or non-responders.

Figure 94: Mean HAQ by EULAR response category for those receiving bDMARDs



Statistical analyses have been undertaken for those patients who have a good or moderate EULAR response. No formal analysis was conducted for those patients who had no EULAR response as they are assumed to have treatment stopped after six months in accordance with NICE guidance within the cost-effectiveness analyses.

An "Autoregressive Latent Trajectory (ALT) model" (Bollen & Curran 2004[273]) was fitted separately for moderate and good responders. The model uses baseline characteristics, including baseline HAQ, to estimate both initial HAQ response (6 months) and the longer term progression of HAQ in a single statistical model. The model incorporates a random intercept and a random slope from a growth model which captures the fixed and random effects of the latent growth trajectories over time. It also includes an autoregressive structure representing any time specific influences between the repeated measures of HAQ over time. The model can be written as follows:

$$y_{it} = \eta_{0i} + \eta_{1i}x_t + \rho_t y_{it-1} + \varepsilon_{it} \qquad t = 1, \dots, 6$$

$$y_{i0} = \gamma_0 + w'_i\boldsymbol{\gamma_1} + \varepsilon_{i0}$$

$$\eta_{0i} = \alpha_0 + w'_i\boldsymbol{\beta_0} + u_{0i}$$

$$\eta_{1i} = \alpha_1 + w'_i\boldsymbol{\beta_1} + u_{1i}$$

where y_{it} denotes HAQ for patient i at time t for $t = 1, \dots, 6$ (where $t = 1$ corresponds to 6 months after starting biologic, $t = 2$ corresponds to 12 months after, etc.); η_{0i} and η_{1i} are a random intercept and a random slope respectively; w'_i is a time invariant, individual specific vector of baseline covariates; x_t are the time scores of a nonlinear trend where, for identification purposes, we set the first one to zero ($x_1 = 0$) and the last one, thirty months

later, to 3 ($x_6 = 3$) and freely estimate the remaining time scores ($x_2, \dots, x_5$). If a linear trend can appropriately describe the data the estimated time scores should follow the sequence 0.6, 1.2, 1.8, 2.4 for successive periods $t = 2, \dots, 5$. The ε_{it} are mean zero normal disturbances with time varying variances equal to $\sigma^2_{\varepsilon t}$, they are independent over time and uncorrelated with the $u_i's$. The $u_i's$ are mean zero, normally distributed, time invariant individual random terms with a full covariance matrix and potentially correlated with ε_{i0}.The parameters $\gamma_0, \alpha_0, \alpha_1$ and the vectors of parameters $\boldsymbol{\gamma_1}, \boldsymbol{\beta_0}, \boldsymbol{\beta_1}$ are fixed over time whereas ρ_t is a time varying parameter.

HAQ at baseline is treated as predetermined. Baseline covariates, w'_i, include: age; gender; disease duration (in months); DAS28 score; and number of previous DMARDS. The continuous baseline covariates are centred around their overall sample means (see Table 189). In addition the covariate age is divided by 10 in the model to avoid convergence problems due to scaling differences. This is for ease of interpretation of the estimated parameters but does not change the model in any way.

Table 189: Sample means of baseline covariates

	All sample	Moderate responders	Good responders
Covariate	Sample mean (n = 10186)	Sample mean (n = 5492)	Sample mean (n = 2417)
Age	56.096	56.854	53.815
Female	0.763	0.781	0.700
Disease duration (months)	159.444	160.188	155.544
DAS score	6.551	6.763	6.281
Number of previous DMARDS	3.898	3.937	3.645

We estimate the model using maximum likelihood with robust standard errors (sandwich estimators) to guard against non-normality. Initially a joint model for the three groups (good EULAR response; moderate EULAR response and no EULAR response) was estimated to try to maximise informative data. However, it was found that no restrictions across groups could be imposed and thus the final models had to be estimated conditional on EULAR response to therapy at 6 months. Table 190 shows the estimated parameters of the models for moderate and good responders.

Table 190: Estimated parameters and standard errors in brackets

		Moderate		Good	
	x_2	0.159	(0.397)	1.649	(1.531)
	x_3	1.634***	(0.314)	2.515***	(4.395)
	x_4	2.732***	(0.351)	3.260***	(12.639)
	x_5	3.249***	(0.415)	2.810***	(6.998)
Random intercept (η_{0i})	Intercept	1.365***	0.05	1.233***	0.112
	(Age – mean age)/10	0.088***	0.008	0.147***	0.014
	Female	0.161***	0.021	0.145***	0.035
	Disease duration (months) – mean disease duration	0.006***	0.001	0.013***	0.002
	DAS score – mean DAS score	0.097***	0.010	0.091***	0.021
	Number of previous DMARDS – mean number of previous DMARDs	0.044***	0.005	0.106***	0.013
Random slope (η_{1i})	Intercept	0.043	0.03	-0.091**	0.042
	(Age – mean age)/10	0.009***	0.003	-0.009*	0.005
	Female	0.009*	0.006	0.003	0.008
	Disease duration (months) – mean disease duration	0.000	0.000	-0.001***	0.000
	DAS score – mean DAS score	0.003	0.003	-0.011*	0.006
	Number of previous DMARDS – mean number of previous DMARDs	0.004**	0.002	-0.007*	0.004
HAQ at baseline	Intercept	1.915***	0.015	1.797***	0.023
	(Age – mean age)/10	0.052***	0.006	0.069***	0.010

	Female	0.155***	0.017	0.139***	0.027
	Disease duration (months) – mean disease duration	0.004***	0.001	0.006***	0.001
	DAS score – mean DAS score	0.179***	0.007	0.158***	0.013
	Number of previous DMARDS – mean number of previous DMARDs	0.033***	0.004	0.076***	0.008
	ρ_1	0.111***	0.025	0.007	0.058
	ρ_2	0.117***	0.034	0.129**	0.052
	ρ_3	0.069***	0.021	0.182***	0.046
	ρ_4	0.040	0.033	0.246***	0.055
	ρ_5	0.019	0.047	0.216***	0.041
	ρ_6	0.026	0.040	0.225***	0.052
Cov	HAQ0 - η_{0i}	0.171***	0.008	0.241***	0.022
	HAQ0 - η_{1i}	0.005	0.004	-0.018**	0.008
	η_{0i} - η_{1i}	0.005	0.006	-0.039**	0.019
	Var(η_{0i})	0.259	0.017	0.431	0.067
	Var(η_{1i})	0.004	0.001	0.009	0.005
var	Eps0	0.245***	0.006	0.335***	0.010
	Eps1	0.069***	0.008	0.039	0.041
	Eps2	0.050***	0.003	0.074***	0.011
	Eps3	0.058***	0.005	0.073***	0.007
	Eps4	0.044***	0.004	0.072***	0.010
	Eps5	0.047***	0.007	0.060***	0.008
	Eps6	0.053***	0.005	0.065*	0.010
*** P<0.01; ** P<0.05; *P<0.1					

The ALT model fits better than both the autoregressive model and the growth model on their own. Restrictions are tested using the Satorra-Bentler[274] scaled difference chi-square test.

As discussed above, the model provided estimates very close to the observed data in terms of 6 month HAQ changes. The cost effectiveness model used estimates of the 6 month HAQ change for a patient with mean characteristics of the overall sample, baseline HAQ of 2.03,

with all error terms set to zero and conditional on EULAR response category. This resulted in estimates of 0.317 (se 0.048) for moderate responders and 0.673 (se 0.112) for Good responders.

cDMARDs

Norton *et al.* estimated[270] HAQ progression in patients not receiving bDMARDs using data from patients recruited to the ERAS inception cohort study. Observations relate to patients recruited between 1986 and 1998 (n=1460), followed for 10 years, and a growth mixture model approach was taken. In the published paper, four classes were identified. These findings have been corroborated in the NOAR dataset with follow up to 15 years and the ERAN dataset.[271] Whilst the concern in the cost effectiveness analysis is to estimate the expected change in HAQ over time, not with the latent classes per se, the latent class analysis provides a more flexible approach as it allows the incorporation of patient characteristics as predictors of HAQ progression in a more appropriate manner. Importanlty, it also provides a reflection of how the rate of HAQ progression changes over time and places no restriction on this being a simple linear progression. This is likely to be a more approropriate reflection of a chronic disease, the use of different treatments (including drugs and surgical interventions) at diferent points in the care pathway which influence that progression and the nature of the HAQ scale itself. The use of a simple annual progression rate for all patients at all time points does none of these things.

A modified analysis based on the published Norton et al study was performed so that the patient descriptors used within the cost effectiveness model were used as covariates within the statistical model as explanatory variables for group membership. In this way, the expected HAQ at any point for a patient with a given set of baseline characteristics can be estimated. The model is formally :

$$y^*_{itc} = \eta_{0ic} + \eta_{1ic}x_t + \eta_{2ic}x_t^2 + \eta_{3ic}x_t^3 + \varepsilon_{it} \qquad t = 0,0.5,1,2,\dots,15$$

$$y_{itc} = \begin{cases} y^*_{itc}\ if y^*_{itc} > 0 \\ 0\ if\ y^*_{itc} \leq 0 \end{cases}$$

Where *c* is the class and the probabilities of class membership are estimated using a multinomial logit model:

$$\Pr(C_{it} = c|z_{it}) = \frac{e^{z_{it}\mu c}}{\sum_{s=1}^{4} e^{z_{it}\mu s}}$$

Where z contains a series of factors as covariates within the model that were originally considered in separate analyses in Norton et al. [275] plus additional factors relevant to our

decision model (Age at disease onset, Female, deprivation level, disease duration, rheumatoid factor positive at baseline, fulfilment of ACR criteria at baseline, baseline DAS, failed two DMARDS, DAS response achieved at 6 months).

A replication of the four classes established by Norton et al is shown in Figure 95 along with validation in the NOAR and ERAN datasets. Probabilities in this case relate to the study populations as whole, not those relevant to the decision problems considered int his report. This is marked as academic-in-confidence

[redacted]

The plots show that there are clearly identifiable separate groups in terms of HAQ progression. Three classes exhibit a J-shaped curve and the fourth shows a general worsening over time. In all cases, the rate of worsening over time decreases. This is directly contrary to the typical assumptions of DMARD worsening incorporated into cost effectiveness models. The use of the growth model also avoids the prediction that large proportions of patients progress to the worst HAQ state (3) before death. This is contrary to the pattern seen in observational datasets both in ERAS/ERAN/NOAR and beyond. For example, in the US NDB just 1% of observations exceed a HAQ of 2.5 (cite Hernandez et al MDM in press). Whilst there may be reasons why observational datasets like this do not fully represent patients with such extreme levels of functional disability (e.g. that self completed surveys are not returned) it is unlikely that these are substantially biased.

There are limitations with this approach: ERAS is an inception cohort with follow-up of patients up to 15 years and we therefore cannot be sure what happens beyond that time. Covariates refer to baseline characteristics in the ERAS dataset and, whilst many of these are set, this baseline does not match all the uses of the data in the cost effectiveness analysis. It should be noted however that many of the limitations that are pertinent to the ERAS analysis are similarly applicable, often to a greater degree, in the studies that underpin the mean HAQ progression rates that are typically used in cost effectiveness analyses of drug therapies in RA.

The methods used by the Assessment Group differ from those used by the manufacturers which typically assume within their base cases that HAQ progression on bDMARDs is zero, and that HAQ progression on cDMARDs is at the rate of 0.045 per annum.

As seen in Figure 93 the assumption that there is no HAQ progression whilst on bDMARDs appears, in the short term, to be supported by the data from the BSRBR, but however the assumed progression on cDMARDs is not as seen in Figure 94.

Calculating an accurate HAQ progression can be challenging as: historical data on past trends may only be a weak predictor of future trajectories; and there are no data on patients who are inadequately treated. In addition, HAQ alone may not encompass all utility impacts of RA that can be caused by flares.

The Assessment Group identified three papers that provided detail on HAQ trajectory whilst patients were receiving cDMARDs.[217,276,277] The search was not systematic and it is possible that papers were not identified. Key elements of these trials have been tabulated (Table 191). It is also not known whether the use of current cDMARDs would be associated with a lower HAQ trajectory.

Table 191: Identified evidence on HAQ progressions whilst on cDMARDs.

Publication	Number of patients analysed	cDMARDs	Mean follow-up (years)	Average HAQ progression per annum
Plant et al[276]	421	hydroxychloroquine, sodium aurothiomalate, auranofin and penicillamine	5	0.08 (from years 1 to 5)
Symmons et al[277]	466	Intensive cDMARD treatment	3	0.06
Munro et al[217]	440	Intramuscular gold	5	0.05 (from years 2 to 5)

The clinical advisors within the Assessment Group stated that observational studies of RA populations generally show a HAQ progression substantially below 0.50 per year, but caution that these often cover the spectrum of RA patients and would contain patients who would not have received bDMARDs. This point is highlighted in Williams et al.[278]

In order to provide an insight into the impact of assumed HAQ trajectory whilst on cDMARDs the Assessment Group have undertaken scenario analyses using the values of 0.045 for cDMARDs and 0.06 for palliative care in addition to using the models derived from the ERAS database.

There appears to be little long-term evidence to support the value used by the manufacturers; in contrast the values used by the Assessment group have come from a large, prospective, observational database that has been corroborated in a separate database. Assuming a linear HAQ progression does not take into account the impact of surgery which may halt HAQ progression, the costs of which are currently assumed to be incurred without benefit.

6.3.15 Time to discontinuation on treatment

The duration of treatment on the first biologic for adult RA patients was estimated using the BSRBR database which records the dates on which therapies are initiated and ended. Separate analyses were undertaken for those patients obtaining good and moderate EULAR responses at 6 months. Patients classed as non-responders at 6 months are assumed to be withdrawn from therapy in the AG model (as in current NICE guidance which requires an improvement

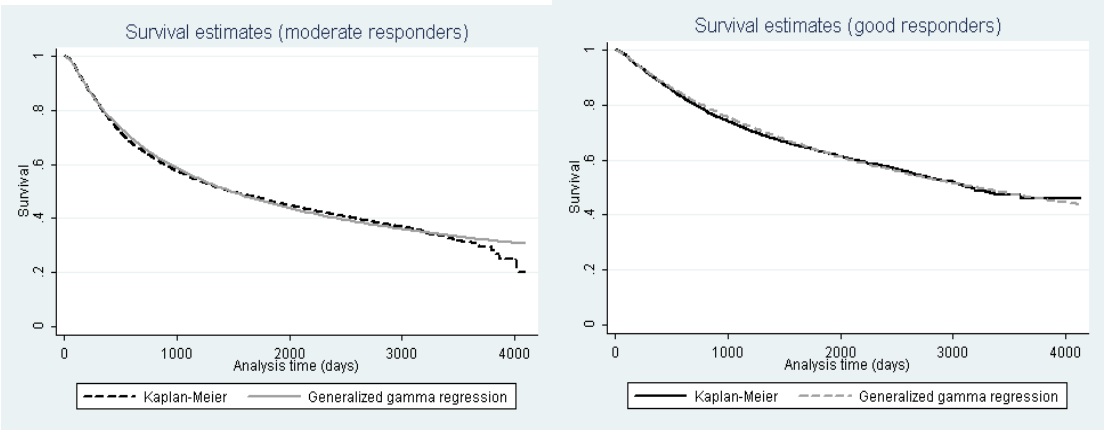
in DAS28 of at least 1.2 at this time point for treatment to be maintained). This allows patients that have been withdrawn prior to 6 months to be included in the analysis, though there is a risk that their response category recorded at 6 months is in fact related to having switched to some other therapy.

A range of parametric survival models (Weibull, exponential, gompertz, loglogistic, lognormal, gamma and Weibull frailty models) were considered. The best fitting model, in terms of both Akaike information criterion (AIC) and the Bayesian Information criteria (BIC) was that based on the gamma distribution. The following covariates were included: age; gender; disease duration at baseline; DAS score; number of previous DMARDs; and HAQ at baseline. We included all covariates, even if insignificant, but considered alternative specifications (such as squared and log terms) in order to identify our preferred model, guided by AIC/BIC.

Establishing separate covariates for the individual biologic therapies within this appraisal was considered. Since golimumab, abatacept, tocilizumab and certolizumab pegol comprised less that 1% of the observations, and had follow-up durations of much shorter duration, these were excluded leaving only infliximab, etanercept and adalimumab. Whilst the duration of treatment for those on etanercept and adalimumab was significantly shorter than for infliximab, this is likely to be due to the times at which therapies became available in the UK. Due to this potential confounding and the lack of data for a number of treatments, separate terms for individual therapies in the cost effectiveness analysis were not adopted.

Two plots comparing the duration on treatment estimated by the models to those observed in the BSRBR database are shown in Figure 96. These are divided into those patients with moderate or good EULAR response, and are constrained to only those patients who would be eligible for biologics under current NICE guidance. Patients who met the NICE criteria were the overwhelming majority and comprised 7250 of the 7743 patients (94%).

Figure 96: Plots of the estimated data from the statistical models compared with the observed data



a) Moderate responders (NICE eligible) b) Good responders (NICE eligible)

Given the paucity of data on bDMARDs used before cDMARDs an assumption was required regarding the duration on treatment if bDMARDs were used before cDMARDs. It was assumed that the duration would be unaffected by whether or not cDMARDs were used prior to bDMARDs.

There were also little data on the duration of response for patients receiving cDMARDs. Based on the assumption that cDMARDs are not likely to be more toxic than biologics used in combination with a cDMARD, it was assumed that the survival duration for each EULAR response category for bDMARDs would be applicable for cDMARDs.

It was assumed that patients would not switch to a subsequent treatment within six months of initiating a treatment, this assumes that any adverse event would be monitored before changing treatment at six months.

The method used by the Assessment Group differs from those of the manufacturers but it is commented that there was diversity in the methods used by the manufacturers with no clear consensus reached. One flaw in the approach taken by manufacturers is that the discontinuation rates had frequently not been conditional on EULAR response and thus the average time on treeatment would be decreased by those patients without a response who typically stay on treatment for one year, despite the current NICE stopping criteria.

In summary the Assessment Group does not believe any of the methods assumed by the manufacturers represents a significantly better method than that used by the Assessment

Group and there is a reason to believe that the approach taken by the Assessment Group is the prefered method.

6.3.16 Rebound post-treatment

The change in a patient's HAQ when treatment has failed to be efficacious or is stopped due to an adverse event is not known with certainty. The Assessment Group has assumed that following cessation of treatment the initial HAQ-improvement experienced on treatment initiation would be lost. The resultant HAQ would be assumed for the subsequent six months when the next treatment in the sequence is trialled.

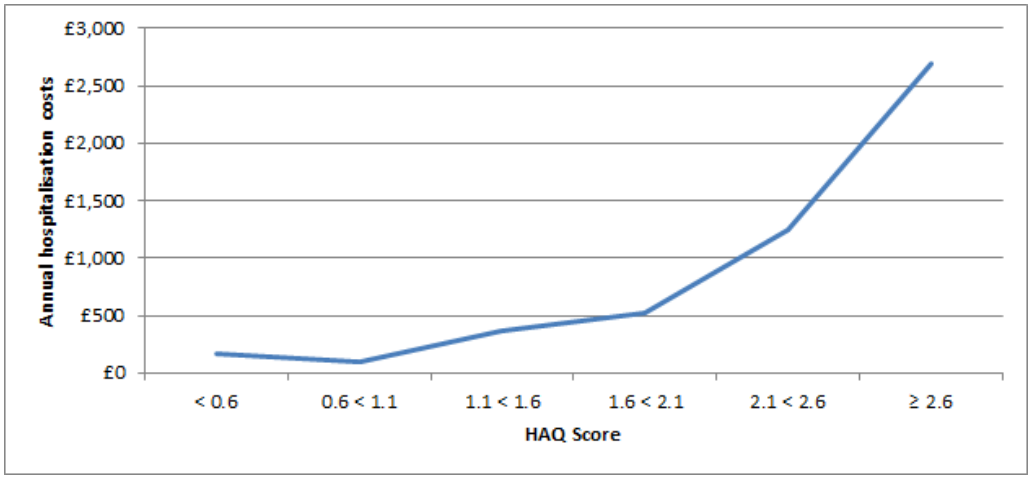
This is is similar to assumptions made within the manufacturers' models

6.3.17 Assumed NHS costs per HAQ band

A brief review of the recent literature regarding the costs associated with active RA and in particular HAQ score identified few data that were not identified collectively within the manufacturers' submissions. The only information of note was a poster by Bansback et al.[279] which using Canadian data concluded that 'the study finds no signal after three years that biologic therapies in patients with RA have led to overall cost offsets from related treatment costs'. Possible explanations that were proffered were: falling resource utilization in general, potentially due to more aggressive use of cDMARDs, have given a false impression that biologics are causally associated with resource utilization; that cost offsets occur beyond three years; and that the model is mis-specified and estimates remain biased.

Whilst these results are noted the Assessment Group believe it is plausible that there could be an increase in hospitalisation costs as HAQ increases. Having reviewed the hospital costs within the manufacturers' submissions the AG decided to use that reported by Abbvie for the base case, which were amongst the lowest of those presented and were relatively flat until the patient had severe HAQ scores (defined as HAQ scores of 2.125 and greater). These values were derived from data taken from the NOAR database on impatient days and joint replacements[238,280] and were multiplied by NHS reference costs. The values assumed in the Assessment Group base case are depicted in Figure 97.

Figure 97: The assumed relationship between annual hospitalisation costs and HAQ score in the AG model



6.3.18 Utility related to HAQ

The NICE Methods guide states that mapping is an acceptable method for estimating EQ-5D from clinical outcome measures in the absence of direct evidence, but that the statistical properties of the model "should be fully described, its choice justified, and it should be adequately demonstrated how well the function fits the data." (page 39-40)[199]. UCB (certolizumab pegol) provided data on the changes in EQ-5D in the initial six-month period but these were marked academic-in-confidence.

Hernandez et al., (2013a,[281] 2013b[282]) report the results of fitting a bespoke mixture model to data from patients with RA from a US observational database comprising in excess of 100,000 observations. Full details of the dataset, the statistical model and its performance (in comparative and absolute terms) are provided in the manuscripts.

The set of models reported include HAQ, HAQ^2, pain, age, age^2 and gender as explanatory variables. These were included because models performed substantially better when they are included. Most previous analyses have excluded pain. However, a substantially better estimate of EQ-5D is obtained by the inclusion of pain alongside HAQ than via HAQ alone. This is to be expected since the domains covered by the HAQ instrument are very similar to the domains of usual activities, mobility and self-care in the EQ-5D. The dimension of "pain" attracts the highest weights in the EQ-5D UK scoring regression. The fact that pain enters as a separate covariate in the Hernandez model is because HAQ and pain are not perfectly correlated. It is therefore important to include pain as an explanatory variable in estimating EQ-5D.

This does not mean that the cost effectiveness model need to be both HAQ and pain based, or that separate HAQ and pain treatment effects need to be estimated for therapies. There are alternative methods by which the relationship between HAQ and pain can be incorporated in to the cost effectiveness model without the requirement for additional complexity, rather than reverting to poorer methods of explaining EQ-5D.

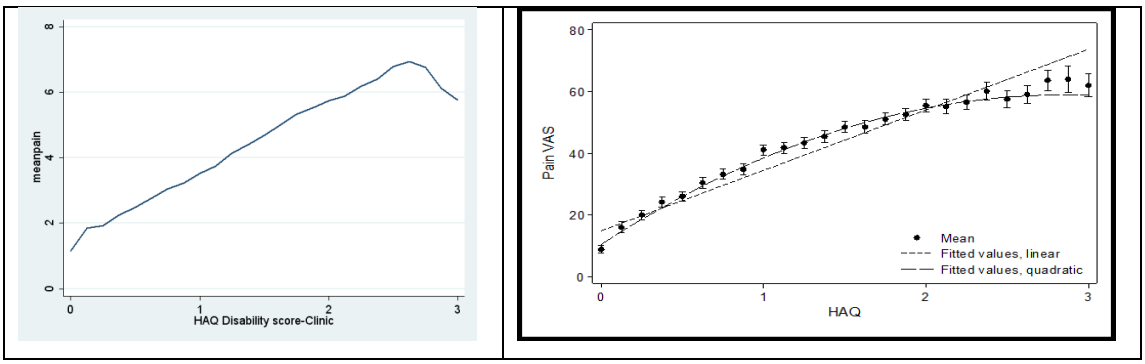
The Assessment Group use a two-step process for estimating EQ-5D values from HAQ values: the first step simulates the expected pain score associated with HAQ; the second step estimates EQ-5D based on both HAQ value and pain score.

Step 1: Simulating the expected pain score associated with HAQ.

The estimation of EQ-5D utility scores is substantially more accurate when based on HAQ and pain than on HAQ alone as detailed in Hernandez Alava et al[253] and Hernandez Alava et al.[253] In order to incorporate the published statistical models that estimate this relationship, pain is independently predicted from the simulated HAQ score for each patient within the model. Whilst this assumes that all treatments affect pain proportionate to their effect on HAQ score this is also the assumption implicit in all models that exclude pain.

HAQ and pain are not related in a simple linear fashion as shown in data from the NDB and data from ERAS (Figure 98) which incorporate 100,398 observations for the NDB and 13,357 from ERAS.

Figure 98: The relationship between HAQ score and pain value



NDB ERAS

Data from ERAS are used to populate the mathematical model, with the mean pain score (and its variance) being estimated for each feasible HAQ score.

Step 2: Estimating EQ-5D based on both HAQ value and pain scores.

It is well recognised that simple linear regression models are inappropriate for estimating EQ-5D values as a function of clinical outcomes. This is because the assumption of conditional normaility does not hold for an outcomes measure that is limited above by full health (1), at the worst health state (-0.594) and which is typically bi- or tri-modal within this range. This theoretical assertion is supported by empirical findings across a broad range of disease areas[283] and within rheumatoid arthritis from two separate large datasets that span the full spectrum of disease.[284] Citing from Hernandez Alava[285] Linear models lead to biased estimates of EQ-5D. They estimate higher EQ-5D scores for patients in severe health states, and lower EQ-5D scores for those patients in less severe health states. The net effect is an undervaluation of the cost effectiveness of effective therapies. This has been shown to be of a substantial magnitude in RA with ICERs varying by up to 20%'.[285]

In this report an alternative method is undertaken, based on mixture models which use an underlying distribution that is bespoke to the EQ-5D UK instrument. This has been reported in Hernandez Alava et al. [285] The model was estimated using data from the US NDB. A total of 103,867 observations were included in the total dataset from 16,011 patients. The size of the dataset dwarfs that which is typical of most "mapping" studies and provides a good exemplar in which to test competing methods because patients spanned the full range of HAQ, pain and EQ-5D values.

The preferred model comprised four components, each of which includes HAQ and HAQ^2, pain, age and age^2 as explanatory variables. HAQ, pain and $pain^2$ enter the model as predictors of component membership. The model fits substantially better than linear regression or response mapping approaches, does not generate non feasible values or suffer from systematic bias in the estimates. Full coefficient values are reported in the associated publications. We used the full covariance matrix to incorporate parameter uncertainty into the cost effectiveness model when running probabilistic sensitivity analyses. These data can be obtained online:
:(http://rheumatology.oxfordjournals.org/content/suppl/2013/01/20/kes400.DC1 - accessed July 2013[286])

The Assessment Group believe that their method is more appropriate than those used by the manufacturers.All of the studies used in the base case manufacturer submissions are based on linear regression models with insufficient information on which to judge the appropriateness of the statistical models being used and with far fewer patients than used to derive the relationship between HAQ, pain and utility used by the Assessment Group.

EQ-5D scores typically demonstrate a non –standard distributional form, which makes standard statistical models inappropriate. The scores are limited above at full health (1) and below (-0.59), are multimodal and there is a gap between full health and any degree of impairment (0.88). It has been shown both in Rheumatoid Arthritis specifically (cite Hernandez et al (2012[284], 2013a[281], 2013b[282]), and a wide range of other disease areas[283] that models typically applied in the "mapping" literature, and most typically this is the linear regression model, are biased. They tend to underestimate EQ-5D values for patients in good health and undervalue EQ-5D for those in severe health states. This is not a trivial matter – Hernandez et al (in spress) report how the ICER may be affected by up to 20% depending on the severity of patients being modelled.[282]

The NICE DSU funded a study that uses one of the largest observational databases of patients with RA in the world to compare a range of statistical methods. This demonstrated that linear models are biased and should not be used in this setting and that the method adopted by the Assessment Group performed far better than a linear model. Critically, this dataset includes patients across the entire range of disease severity.

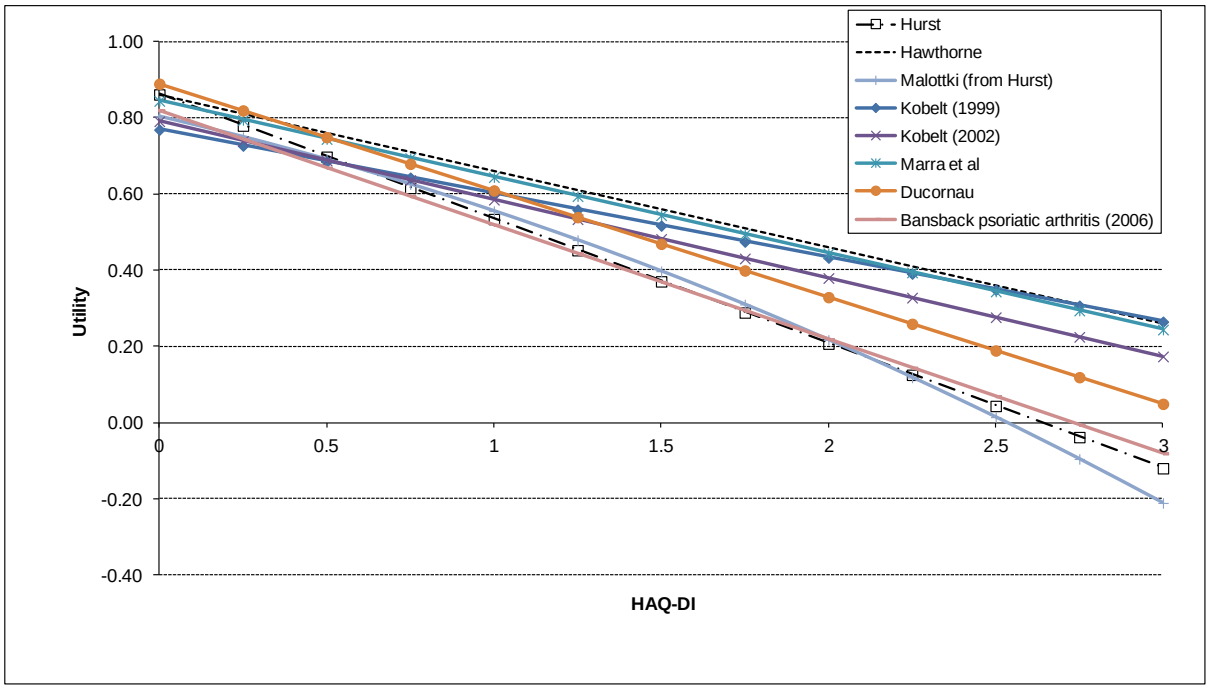
The Assessment Group report that there are further studies that could have been used to inform the manufacturers' submissions that report on the relationship between health utilities, HAQ and other covariates. These are briefly summarised.

- Hawthorne et al (2000) used UK EQ-5D data from 139 patients with RA recruited in Australia in a linear regression with HAQ as the only covariate[287]
- Lindgren et al (2009) used Swedish registry data from 1787 patients and used the UK EQ-5D tariff to estimate EQ-5D as a function of HAQ, DAS and age[263]
- Marra et al (2007) [168] report UK tariff EQ-5D as a function of HAQ and age (n=317) from a sample of Canadian patients with RA
- Kobelt et al (1999, 2002) reports mean EQ-5D scores by HAQ category using Swedish registry data (n=116) in the former paper and a combination of Swedish and UK patients in the latter (n=210). For illustrative purposes only, we fitted simple linear models to these reported mean values.

Compared to these studies, the models used as the base case for the entire set of manufacturer submissions (Hurst[213], Malottki[202], Duccournau [243] and Bansback[252]) have a greater assumed

impact on utility than the remaining studies particularly where HAQ exceeds 2 which is the case for a sizeable proportion of cDMARD treated patients given the assumptions used in many of the costs effectiveness models regarding HAQ progression over time whilst on cDMARDs. (Figure 99).

Figure 99: A comparison of published relationships between utility and HAQ



In a sensitivity analysis the equation mapping HAQ to utility described in Malottki et al was used. Additionally, using the relationship between HAQ and pain taken from the ERAS study (personal communication) rather than that from the NDB was evaluated.

6.3.19 The assumed costs and disutilities associated with adverse events.

The Assessment Group took a simplistic view regarding adverse events.

It was assumed that only serious infections would carry a significant cost and disutility burden and limited the adverse events within the model to serious infections alone. A review of the adverse effects of biologics[288] indicated that serious infections were observed in 35 per 1000 patients (95% CI: 27 to 46) It was assumed that the rate of serious infection was independent of the bDMARDS used. Singh et al reported the rate of serious infections in people on cDMARDs to be 26 per 1000 patients no CI reported), impying that an additional 9 per 1000 patients would sustain a serious infection when using a bDMARD.

The costs (£1479 per episode) and undiscounted QALY loss associated with serious infections (a loss in utility of 0.156 for 28 days) were both taken from the Pfizer submission.[183] Costs and QALY losses (assumed to be 0.012 per episode). Based on the assumed increased rate of serious infection it was assumed that a bDMARD strategy would incur an additional £13.31 and a QALY loss of 0.0001 per typical patient treated. These values were increased 100-fold in sensitivity analyses to assess the impact of events that may be too infrequent to be observed in RCTs, but may become apparent when large numbers of patients are treated.

The majority of submissions excluded adverse events from the model, although Pfizer included both costs and disutility in a sensitivity analysis and Abbvie included costs alone within the base case.

6.3.20 Mortality Associated with RA

The link between RA and early mortality has been long documented with a seminal paper being that of Wolfe et al.[289] published in 1994. A meta-analysis by Naz and Symmons[5] incorporating 15 studies involving greater than 300 subjects and published between 1993 and 2006 indicated a range in the standardised mortality ratio (SMR) of between 1.01 and 2.70. Dadoun et al.[6] undertook a meta-analysis of studies reporting mortality rates in RA and reported a meta-SMR of 1.47 (95% CI: 1.19;1.83) from eight studies although the level of heterogeneity was high with an I^2 statistic of 93.47.

However, little data have been published on the relationship between change in HAQ and change in expected mortality, which is the key relationship that is required if there is to be proof that a increase in HAQ score is associated with a increase in mortality. Following a literature review, a paper by Michaud et al.,[290] published in 2012 was identified that aimed to establish the relationship between change in HAQ and mortality. Their conclusions were that ‘changes in the PCS [SF36 physical component summary score] and HAQ did not contribute substantially to predictive value over and above the baseline values of these variables”. As such the AG assumed that only the baseline HAQ score was important for predicting mortality and the hazard ratios (HR) detailed in Table 192 were applied. It is noted that as initial HAQ increases then the HRs also increases. It was assumed that these HRs were independent of time.

Table 192: Hazard ratio for mortality associated with HAQ category

Initial HAQ category	Hazard Ratio (95% Confidence Interval)
0.000	1 (1 – 1) referent
0.125 – 0.375	1.4 (1.1 – 1.8)
0.500 – 0.875	1.5 (1.2 – 1.9)
1.000 – 1.375	1.8 (1.4 – 2.2)
1.500 – 1.875	2.7 (2.2 – 3.5)
2.000 – 2.375	4.0 (3.1 – 5.2)
2.500 – 3.000	5.5 (3.9 – 7.7)

The confidence intervals for each HAQ category overlap with the neighbouring category. In order to preserve monotonicity for the HRs, quantile matching was assumed when drawing the HR for each category for each probabilistic sensitivity analysis iteration. The patient was assumed to die midway through their final year.

The Assessment Group method straddles those of the manufacturers in that it applies a fixed hazard ratio for mortality but selects this hazard ratio based on the initial HAQ category of the patient, with those with a worse HAQ dying sooner on average. This contrasts with the methods used of applying a non-HAQ related hazard ratio, and allowing mortality to be determined by current HAQ score. The Assessment Group comment that the data source used to determine their method is much more recent than those used by the manufacturers.

6.3.21 Calculation of the appropriate number of patients to run when generating results

Diagnostic tests were undertaken to assess the appropriate number of patients to run through the Assessment Group model. Construction of the model provided an indication that 3000-5000 simulated patients produced relatively stable ICERs when reproducing an analysis. A test of 10,000 simulated patients wsa undertaken with the discounted costs, discounted QALYs and an ICER compared with an cDMARD alone strategy recorded for two runs. These analyses were undertaken using the base case assumptions in patients with severe RA who were MTX-experienced and who could receive MTX. Bar charts of these data are provided in Figures 100 to 102

Figure 100: Discounted QALYs from two runs of 10,000 simulated patients

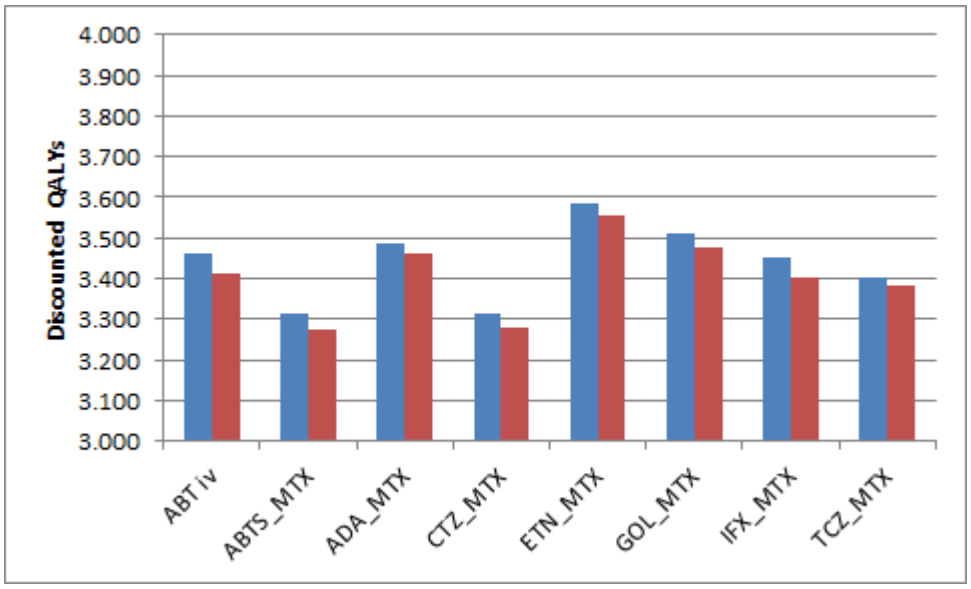


Figure 101: Discounted QALYs from two runs of 10,000 simulated patients

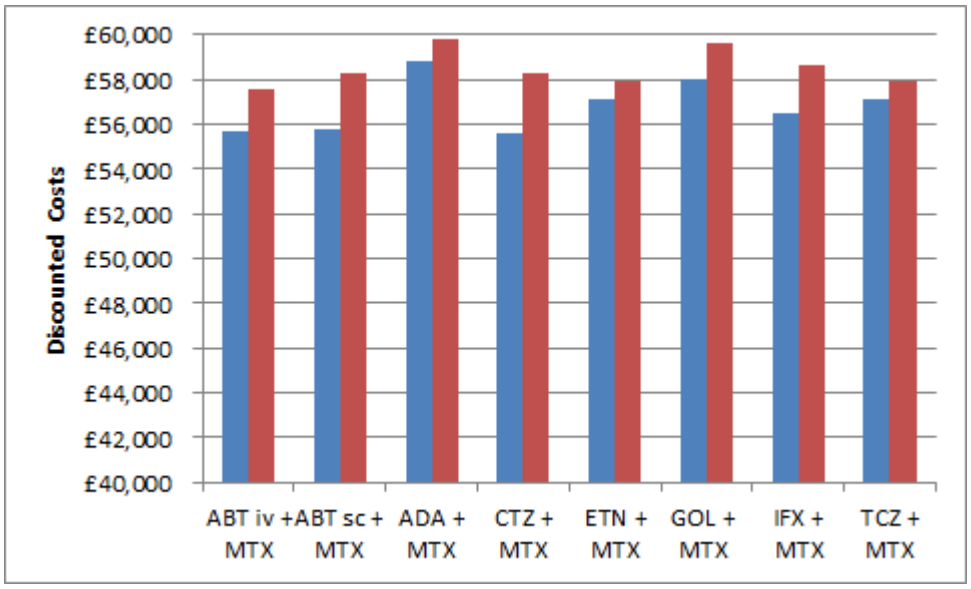
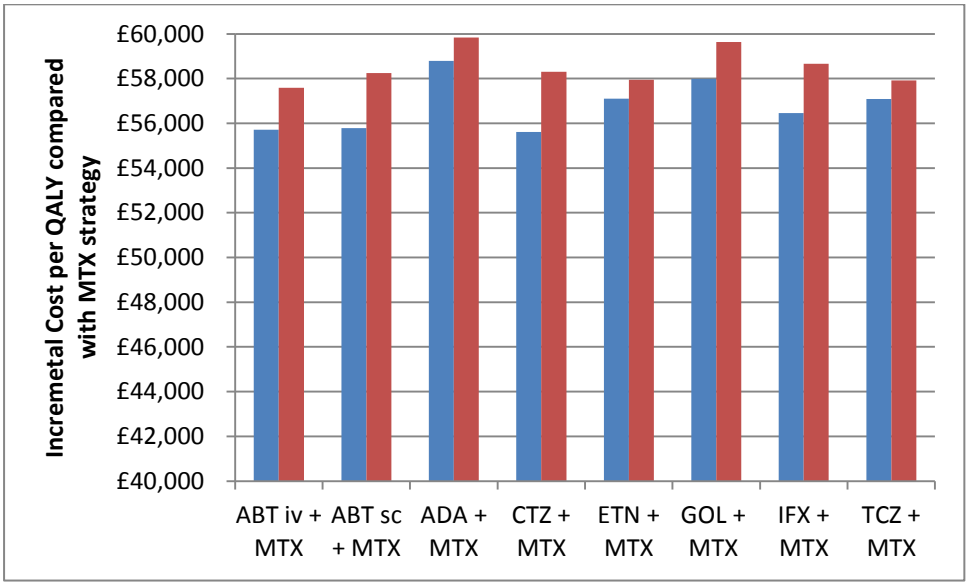


Figure 102: Discounted cost per QALY compared with a cDMARD alone strategy from two runs of 10,000 simulated patients



For patients with moderate RA the computational time required was significantly greater as patients were resampled until the DAS criterion of between 3.1 and 5.2 was met. This led to the results for this group to be taken from 1000 patients. For both the moderate and the severe RA populations the computational time required for a deterministic analysis was approaching 1 hour. For the probabilistic analyses the number of simulated patients was reduced by 90%, (i.e. 1000 for severe patients and 100 for moderate patients) and 100 probabilistic samples were evaluated.

6.3.22 Results

A summary of the analyses undertaken is provided in Table 193. These are all 24 combinations of factors shown excluding those combining EULAR response in MTX-naïve patients as the only data available was for an intervention (golimumab) unlicensed in this population. Each analysis had further sensitivity analyses conducted assessing the: impact of using a different RCT evidence base; a different mapping of HAQ to utility; an increase in the effects of serious adverse events; and a different assumed relationship between HAQ and pain.

Table 193: Combinations of factors analysed in the cost-effectiveness analyses

Population	Treatment provided …	Response Measure	HAQ trajectory on cDMARDs
Population 3 (severe MTX-experienced)	In combination with MTX	EULAR	Taken from the ERAS database
Population 2 (moderate to severe MTX-experienced)	As monotherapy	ACR (then mapped to EULAR)	Using previous NICE appraisal values
Population 1 (severe MTX-naïve)			

Due to the number of results presented the Assessment Group decided that a summary table, providing indicative results would aid the reader. As will be seen there is little difference in the estimated cost-effectiveness of the bDMARDs, with the exception of tocilizumab which differs as it cannot be used after rituximab if it was used as the first bDMARD. As such, the median ICERs in Populations 2 and 3 for all bDMARDs are presented in Tables 194 to 195, which is followed by the full results. It is commented that the ICERs for Population 1 are considerable higher than for Populations 2 and 3.

Whilst full incremental ICERs are provided for Populations 2 and 3, these may be misleading as the ICERs compared with the cDMARD alone strategy are relatively similar. Interventions labelled as dominated may only be slightly more expensive and marginally less effective than a comparator. This cannot be seen in the results as due to the commercial in confidence patient access schemes both discounted costs and discounted QALYs are marked commercial in confidence.

Table 194: Summarised results: Median ICERs for all bDMARD strategies compared with the MTX alone strategy. Populations 2 and 3 who can receive MTX

			Base Case +								
	Response Measure	Assumed HAQ Progression		RCTs with small %ge of bDMARD prior use , adequate MTX-history	RCTs with small %ge of bDMARD prior use (irrespective of MTX-history)	Trials with inadequate MTX history	Malottki mapping of HAQ to utility	Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Relationship between HAQ and pain taken from ERAS	PSA
Population 2 (severe MTX – experienced)	EULAR	ERAS	£56,500	£56,200	£56,900	No data	£60,700	£41,200	£58,500	£96.100	£56,700
		Linear	£33,000	£33,100	£32,800	No data	£35,500	£22,900	£34,700	£63,700	£33,300
	ACR	ERAS	£52,800	£53,400	£55,100	£53,400	£58,900	£38,800	£54,800	£89,500	£53,200
		Linear	£32,100	£31,700	£31,700	£31,700	£34,300	£22,500	£33,100	£59,900	£31,405
Population 3 (moderate MTX-experienced)	EULAR	ERAS	£62,400	£62,000	£65,400	No Data	£65,600	£45,000	£64,200	£68,300	£61,900
		Linear	£34,900	£33,000	£33,900	No Data	£35,400	£21,400	£34,800	£44,500	£33,900
	ACR	ERAS	£61,100	£57,900	£61,100	£74,700	£60,800	£42,300	£62,900	£67,500	£60,100
		Linear	£31,800	£31,100	£31,100	£33,500	£33,400	£22,600	£32,900	£42,700	£31,900
All numbers rounded to the nearest £100.											

Table 195: Summary of median ICERs for all bDMARDs compared with the MTX alone strategy. Populations 2 and 3 who are treated with monotherapy

			Base Case +								
	Response Measure	Assumed HAQ Progression		RCTs with small %ge of bDMARD prior use , adequate MTX-history	RCTs with small %ge of bDMARD prior use (irrespective of MTX-history)	Trials with inadequate MTX history	Malottki mapping of HAQ to utility	Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Relationship between HAQ and pain taken from ERAS	PSA
Population 2 (severe MTX – experienced)	EULAR	ERAS	£73,500	£76,600	£79,800	No data	£80,700	£54,200	£75,700	£125,700	£76,100
		Linear	£38,500	£38,300	£39,000	No data	£41,600	£27,300	£38,500	£74,800	£39,700
	ACR	ERAS	£65,600	£65,200	£77,400	£65,800	£70,600	£46,300	£67,500	£111,200	£65,300
		Linear	£36,500	£35,800	£35,500	£36,400	£38,400	£25,000	£36,000	£69,600	£35,500
Population 3 (moderate MTX-experienced)	EULAR	ERAS	£75,700	£81,500	£80,000	No data	£75,000	£77,600	£75,700	£95,000	£76,400
		Linear	£36,900	£38,600	£35,600	No data	£38,200	£55,300	£36,900	£55,300	£37,700
	ACR	ERAS	£69,800	£70,200	£84,900	£70,700	£69,200	£50,000	£71,600	£81,100	£73,100
		Linear	£36,000	£37,200	£35,100	£35,800	£37,700	£24,700	£36,000	£50,700	£35,400
All numbers rounded to the nearest £100.											

6.3.22.1 EULAR response measure: ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

Table 196: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 56,522	Ext Dominated
ABT iv + MTX	[redacted]	[redacted]	£ 54,727	£ 54,727
IFX + MTX	[redacted]	[redacted]	£ 56,373	Dominated
ADA + MTX	[redacted]	[redacted]	£ 58,217	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 57,633	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 56,476	£ 71,530

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £54,000 to £59,000

Table 197: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population.

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 55,749	Ext Dominated
IFX + MTX	[redacted]	[redacted]	£ 56,009	Ext Dominated
ABT iv + MTX	[redacted]	[redacted]	£ 54,809	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 58,247	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 57,259	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 56,396	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 54,105	£ 54,105

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 198: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 56,244	Ext Dominated
ABT iv + MTX	[redacted]	[redacted]	£ 55,367	Ext Dominated
IFX + MTX	[redacted]	[redacted]	£ 56,944	Dominated
ADA + MTX	[redacted]	[redacted]	£ 58,799	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 57,833	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 56,836	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 54,826	£ 54,826

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 199: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 60,505	Ext Dominated
ABT iv + MTX	[redacted]	[redacted]	£ 58,740	£ 58,740
IFX + MTX	[redacted]	[redacted]	£ 60,931	Dominated
ADA + MTX	[redacted]	[redacted]	£ 62,460	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 61,526	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 60,339	£ 73,496

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 200: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 41,679	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 39,268	£ 39,268
IFX_MTX	[redacted]	[redacted]	£ 40,314	Dominated
ADA_MTX	[redacted]	[redacted]	£ 41,811	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 41,342	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 41,007	£ 56,597

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 201: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 58,497	Ext Dominated
ABT iv + MTX	[redacted]	[redacted]	£ 56,603	£ 56,603
IFX + MTX	[redacted]	[redacted]	£ 58,308	Dominated
ADA + MTX	[redacted]	[redacted]	£ 60,064	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 59,454	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 58,171	£ 71,530

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 202: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
CTZ_MTX	[redacted]	[redacted]	£ 96,517	Dominated
TCZ_MTX	[redacted]	[redacted]	£ 96,111	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 94,099	£ 94,099
IFX_MTX	[redacted]	[redacted]	£ 98,595	Dominated
ADA_MTX	[redacted]	[redacted]	£101,061	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 98,315	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 95,685	£ 107,073

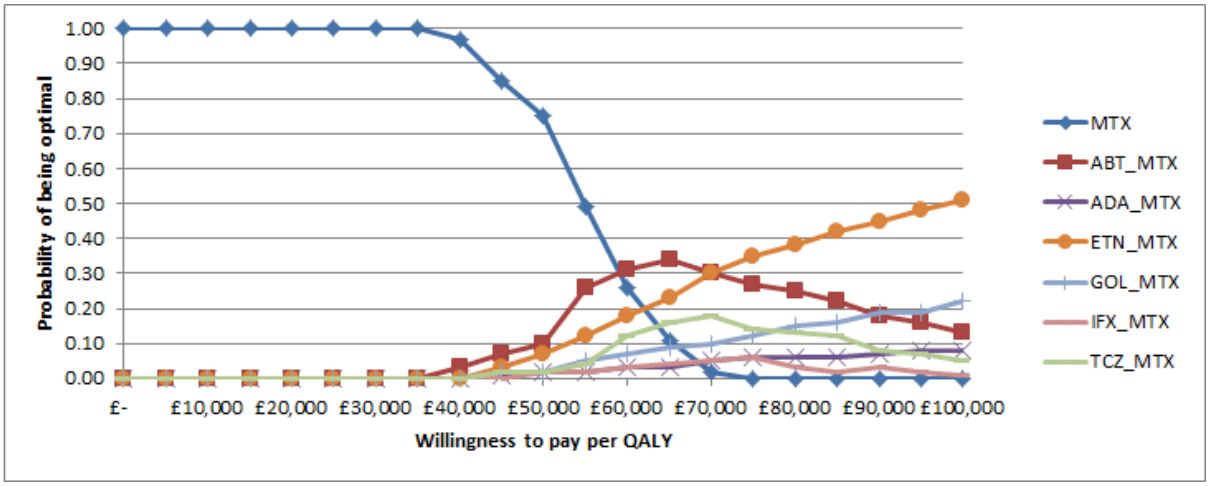
ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 203: Probabilistic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 55,133	Dominated
ABT_MTX	[redacted]	[redacted]	£ 54,781	£ 54,781
IFX_MTX	[redacted]	[redacted]	£ 56,920	Dominated
ADA_MTX	[redacted]	[redacted]	£ 58,202	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 56,979	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 56,410	£ 69,398

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 103: The CEAC when using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population.



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.2 EULAR response measure: Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

Table 204: Deterministic base case results using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
ABT + MTX	[redacted]	[redacted]	£ 31,381	£ 31,381
TCZ + MTX	[redacted]	[redacted]	£ 31,927	Dominated
IFX + MTX	[redacted]	[redacted]	£ 32,322	Dominated
ADA + MTX	[redacted]	[redacted]	£ 34,004	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 33,695	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 33,694	£ 60,756

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £30,000 to £35,000

Table 205: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 31,342	£ 31,342
ABT + MTX	[redacted]	[redacted]	£ 31,725	Ext Dominated
IFX + MTX	[redacted]	[redacted]	£ 32,504	Dominated
ADA + MTX	[redacted]	[redacted]	£ 34,216	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 34,002	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 34,303	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 33,630	£ 45,349

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 206: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 31,679	Ext Dominated
ABT + MTX	[redacted]	[redacted]	£ 31,414	£ 31,414
IFX + MTX	[redacted]	[redacted]	£ 32,295	Dominated
ADA + MTX	[redacted]	[redacted]	£ 33,968	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 33,588	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 33,841	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 33,216	£ 44,385

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 207: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 34,844	Ext Dominated
ABT + MTX	[redacted]	[redacted]	£ 34,252	£ 34,252
IFX + MTX	[redacted]	[redacted]	£ 35,465	Dominated
ADA + MTX	[redacted]	[redacted]	£ 37,054	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 36,809	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 37,061	£ 70,763

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 208: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
ABT + MTX	[redacted]	[redacted]	£ 22,013	£ 22,013
TCZ + MTX	[redacted]	[redacted]	£ 22,636	Dominated
IFX + MTX	[redacted]	[redacted]	£ 22,898	Dominated
ADA + MTX	[redacted]	[redacted]	£ 24,128	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 23,917	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 24,159	£ 52,893

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 209: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
ABT + MTX	[redacted]	[redacted]	£ 32,419	£ 32,419
TCZ + MTX	[redacted]	[redacted]	£ 32,987	Dominated
IFX + MTX	[redacted]	[redacted]	£ 33,377	Dominated
ADA + MTX	[redacted]	[redacted]	£ 35,037	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 34,712	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 34,663	£ 60,756

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 210: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 63,917	Dominated
ABT_MTX	[redacted]	[redacted]	£ 59,788	£ 59,788
IFX_MTX	[redacted]	[redacted]	£ 62,734	Dominated
ADA_MTX	[redacted]	[redacted]	£ 65,644	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 64,709	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 63,668	£ 100,757

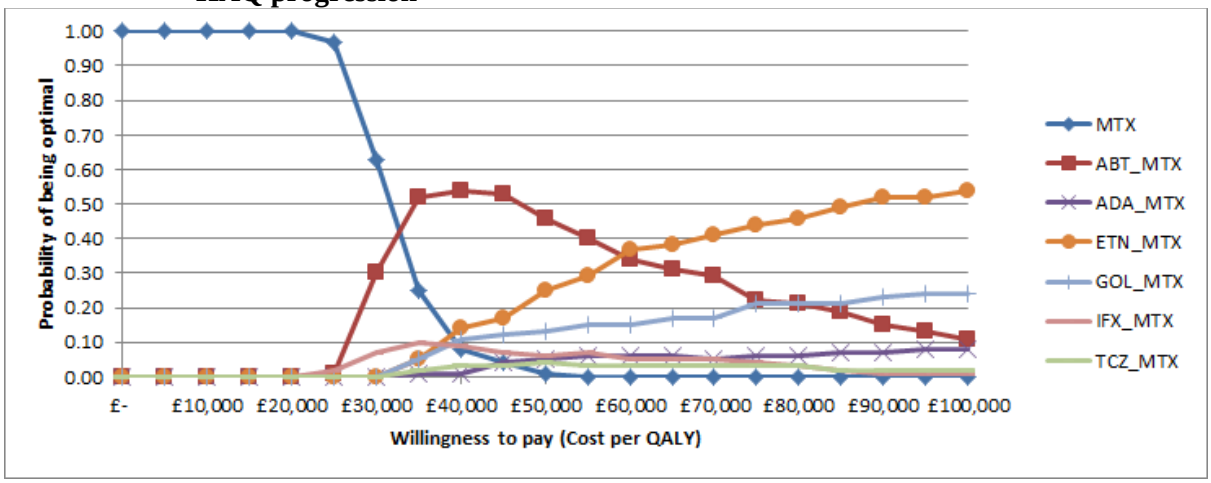
ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 211: Probabilistic base case results using EULAR data directly – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 33,254	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 31,294	£ 31,294
IFX_MTX	[redacted]	[redacted]	£ 32,178	Dominated
ADA_MTX	[redacted]	[redacted]	£ 33,701	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 33,373	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 33,543	£ 58,314

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 104: The CEAC using EULAR data directly and assuming linear CDMARD HAQ progression



The CEAC shows only the probability of being optimal and inferences regarding relative cost-effectiveness shown be made with caution. It is seen however that at a willingness to pay of £30,000 per QALY the MTX strategy has the highest probability of being optimal followed by abatacept + MTX.

6.3.22.3 ACR response measure: ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

Table 212: Deterministic base case results using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 52,857	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 48,730	£ 44,835
IFX_MTX	[redacted]	[redacted]	£ 49,829	£ 121,276
ABTS_MTX	[redacted]	[redacted]	£ 52,694	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 54,043	Dominated
GOL_MTX	[redacted]	[redacted]	£ 52,748	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 53,778	Dominated
ETN_MTX	[redacted]	[redacted]	£ 54,201	£ 214,864

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £52,000 to £55,000

Table 213: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 53,611	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 49,540	£ 49,540
IFX_MTX	[redacted]	[redacted]	£ 50,977	Dominated
ADA_MTX	[redacted]	[redacted]	£ 53,268	Ext Dominated
ABTS_MTX	[redacted]	[redacted]	£ 53,532	Dominated
GOL_MTX	[redacted]	[redacted]	£ 52,856	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 54,345	£ 171,617
CTZ_MTX	[redacted]	[redacted]	£ 54,866	£ 555,949

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 214: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 54,206	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 51,589	£ 51,589
IFX_MTX	[redacted]	[redacted]	£ 52,412	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 55,291	Dominated
ABTS_MTX	[redacted]	[redacted]	£ 55,342	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 54,918	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 56,107	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 56,355	£ 92,435

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 215: Deterministic results having included RCTs with potentially low prior MTX exposure using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 54,444	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 49,944	£ 49,944
IFX_MTX	[redacted]	[redacted]	£ 50,380	£ 94,338
CTZ_MTX	[redacted]	[redacted]	£ 55,077	Dominated
ADA_MTX	[redacted]	[redacted]	£ 53,548	Ext Dominated
ABTS_MTX	[redacted]	[redacted]	£ 53,285	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 53,264	£ 156,861
ETN_MTX	[redacted]	[redacted]	£ 54,767	Dominated

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 216: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 59,026	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 54,827	£ 54,827
IFX_MTX	[redacted]	[redacted]	£ 55,139	£ 83,105
CTZ_MTX	[redacted]	[redacted]	£ 60,419	Dominated
ADA_MTX	[redacted]	[redacted]	£ 58,959	Dominated
GOL_MTX	[redacted]	[redacted]	£ 58,887	Ext Dominated
ABTS_MTX	[redacted]	[redacted]	£ 58,395	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 60,165	£ 231,816

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 217: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 40,008	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 35,832	£ 35,832
IFX_MTX	[redacted]	[redacted]	£ 36,532	£ 92,422
GOL_MTX	[redacted]	[redacted]	£ 38,658	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 38,854	Dominated
ABTS_MTX	[redacted]	[redacted]	£ 38,729	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 39,903	Dominated
ETN_MTX	[redacted]	[redacted]	£ 39,948	£ 445,242

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 218: Deterministic results assuming 100-fold increased impact of adverse events and using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 54,841	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 55,780	Ext Dominated
TCZ_MTX	[redacted]	[redacted]	£ 54,841	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 50,414	£ 36,144
IFX_MTX	[redacted]	[redacted]	£ 51,504	Dominated
ADA_MTX	[redacted]	[redacted]	£ 55,504	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 54,434	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 55,876	£ 153,118

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 219: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 89,552	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 83,832	£ 83,832
IFX_MTX	[redacted]	[redacted]	£ 85,307	£ 193,832
ABTS_MTX	[redacted]	[redacted]	£ 90,255	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 89,203	£ 318,508
CTZ_MTX	[redacted]	[redacted]	£ 91,867	Dominated
ADA_MTX	[redacted]	[redacted]	£ 89,523	Dominated
ETN_MTX	[redacted]	[redacted]	£ 92,310	£ 336,410

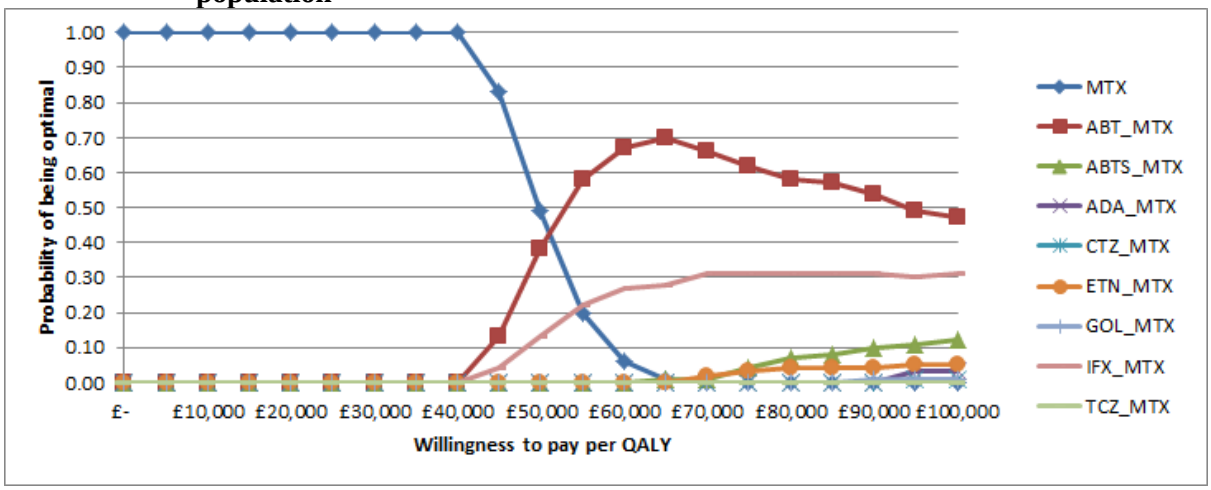
ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 220: Probabilistic base case results using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 53,204	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 49,671	£ 49,671
IFX_MTX	[redacted]	[redacted]	£ 50,560	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 53,216	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 53,493	Dominated
ABTS_MTX	[redacted]	[redacted]	£ 53,104	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 54,403	Dominated
ETN_MTX	[redacted]	[redacted]	£ 54,277	£ 165,441

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 105: The CEAC when using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.4 ACR response measure: Linear HAQ progression and a severe, MTX-experienced, RA population

Table 221: Deterministic base case results using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 32,471	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 29,944	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 29,851	£ 29,851
ABTS_MTX	[redacted]	[redacted]	£ 32,009	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 31,957	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 32,139	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 32,716	Dominated
ETN_MTX	[redacted]	[redacted]	£ 32,997	£ 161,203

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £29,000 to £33,000

Table 222: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 31,908	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 29,621	£ 29,621
IFX_MTX	[redacted]	[redacted]	£ 29,988	£ 76,817
ADA_MTX	[redacted]	[redacted]	£ 31,668	Dominated
ABTS_MTX	[redacted]	[redacted]	£ 31,627	Dominated
GOL_MTX	[redacted]	[redacted]	£ 31,767	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 32,587	£ 104,832
CTZ_MTX	[redacted]	[redacted]	£ 33,053	Dominated

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 223: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 30,967	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 29,051	£ 29,051
IFX_MTX	[redacted]	[redacted]	£ 29,857	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 31,621	Dominated
ABTS_MTX	[redacted]	[redacted]	£ 31,777	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 31,826	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 32,862	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 33,114	£ 68,222

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 224: Deterministic results having included RCTs with potentially low prior MTX exposure using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 32,170	£ 27,467
ABT_MTX	[redacted]	[redacted]	£ 29,321	£ 29,331
IFX_MTX	[redacted]	[redacted]	£ 29,656	£ 138,083
ABTS_MTX	[redacted]	[redacted]	£ 31,756	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 31,736	Dominated
GOL_MTX	[redacted]	[redacted]	£ 31,431	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 32,273	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 32,238	£ 146,211

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 225: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 34,279	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 31,435	£ 31,435
IFX_MTX	[redacted]	[redacted]	£ 32,241	£ 94,210
ADA_MTX	[redacted]	[redacted]	£ 34,371	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 35,016	Dominated
ABTS_MTX	[redacted]	[redacted]	£ 34,404	Dominated
GOL_MTX	[redacted]	[redacted]	£ 34,203	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 35,327	£ 243,480

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 226: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 22,860	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 20,316	£ 20,316
IFX_MTX	[redacted]	[redacted]	£ 21,072	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 22,866	Dominated
GOL_MTX	[redacted]	[redacted]	£ 22,393	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 22,436	Ext Dominated
ABTS_MTX	[redacted]	[redacted]	£ 22,509	Dominated
ETN_MTX	[redacted]	[redacted]	£ 23,015	£ 123,951

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 227: Deterministic results assuming 100-fold increased impact of adverse events and using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 33,656	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 30,943	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 30,842	£ 29,851
ABTS_MTX	[redacted]	[redacted]	£ 33,009	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 32,951	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 33,140	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 33,735	Dominated
ETN_MTX	[redacted]	[redacted]	£ 33,982	£ 161,203

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 228: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 60,689	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 55,382	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 55,529	£ 55,529
ABTS_MTX	[redacted]	[redacted]	£ 59,448	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 59,849	Dominated
GOL_MTX	[redacted]	[redacted]	£ 59,940	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 61,044	Dominated
ETN_MTX	[redacted]	[redacted]	£ 61,196	£ 295,047

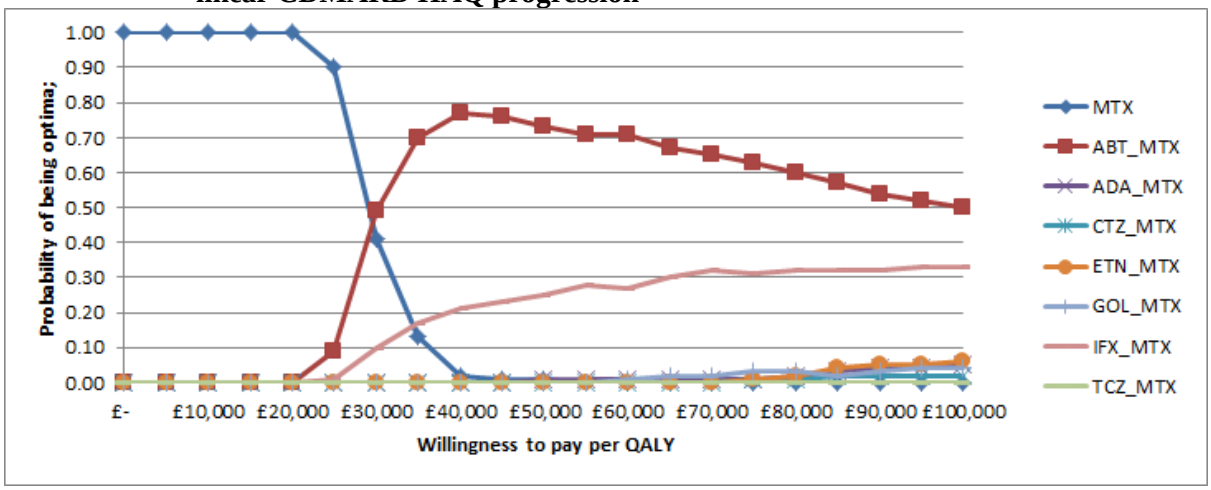
ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 229: Probabilistic base case results using ACR data mapped to EULAR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-
TCZ_MTX	[redacted]	[redacted]	£ 31,481	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 28,829	£ 28,829
ABT_MTX	[redacted]	[redacted]	£ 29,495	Ext Dominated
ABTS_MTX	[redacted]	[redacted]	£ 31,369	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 31,268	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 31,442	Dominated
CTZ_MTX	[redacted]	[redacted]	£ 32,011	Dominated
ETN_MTX	[redacted]	[redacted]	£ 32,255	£ 147,196

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 106: The CEAC using ACR data mapped to EULAR data and assuming linear CDMARD HAQ progression



The CEAC shows only the probability of being optimal and inferences regarding relative cost-effectiveness shown be made with caution. It is seen however that at a willingness to pay of £30,000 per QALY the MTX and the abatacept strategies haver relatively high probabilities of being optimal.

6.3.22.5 EULAR response measure: ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

Table 230: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 58,742	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 58,909	£ 58,909
IFX_MTX	[redacted]	[redacted]	£ 61,311	Dominated
ADA_MTX	[redacted]	[redacted]	£ 63,513	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 63,645	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 62,007	£ 91,315

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £58,000 to £64,000

Table 231: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 61,640	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 59,068	£ 59,068
IFX_MTX	[redacted]	[redacted]	£ 60,143	Dominated
ADA_MTX	[redacted]	[redacted]	£ 62,581	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 62,216	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 62,731	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 60,703	£ 68,887

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 232: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABT_MTX	[redacted]	[redacted]	£ 61,414	£ 61,414
TCZ_MTX	[redacted]	[redacted]	£ 64,727	Dominated
IFX_MTX	[redacted]	[redacted]	£ 65,729	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 64,988	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 67,169	Dominated
ETN_MTX	[redacted]	[redacted]	£ 65,950	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 63,397	£ 73,578

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 233: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 62,901	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 60,110	£ 60,110
IFX_MTX	[redacted]	[redacted]	£ 66,159	Dominated
GOL_MTX	[redacted]	[redacted]	£ 67,917	Dominated
ADA_MTX	[redacted]	[redacted]	£ 67,106	Dominated
ETN_MTX	[redacted]	[redacted]	£ 64,944	£ 143,192

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 234: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
IFX_MTX	[redacted]	[redacted]	£ 42,352	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 42,824	£ 42,824
TCZ_MTX	[redacted]	[redacted]	£ 47,019	Dominated
ADA_MTX	[redacted]	[redacted]	£ 45,051	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 44,991	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 45,148	£ 70,999

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 235: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 60,772	Dominated
ABT_MTX	[redacted]	[redacted]	£ 60,677	£ 60,677
IFX_MTX	[redacted]	[redacted]	£ 63,126	Dominated
ADA_MTX	[redacted]	[redacted]	£ 65,270	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 65,379	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 63,630	£ 91,315

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 236: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABT_MTX	[redacted]	[redacted]	£ 65,431	£ 65,431
TCZ_MTX	[redacted]	[redacted]	£ 67,465	Dominated
IFX_MTX	[redacted]	[redacted]	£ 68,472	Dominated
ADA_MTX	[redacted]	[redacted]	£ 70,607	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 70,091	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 68,042	£ 85,227

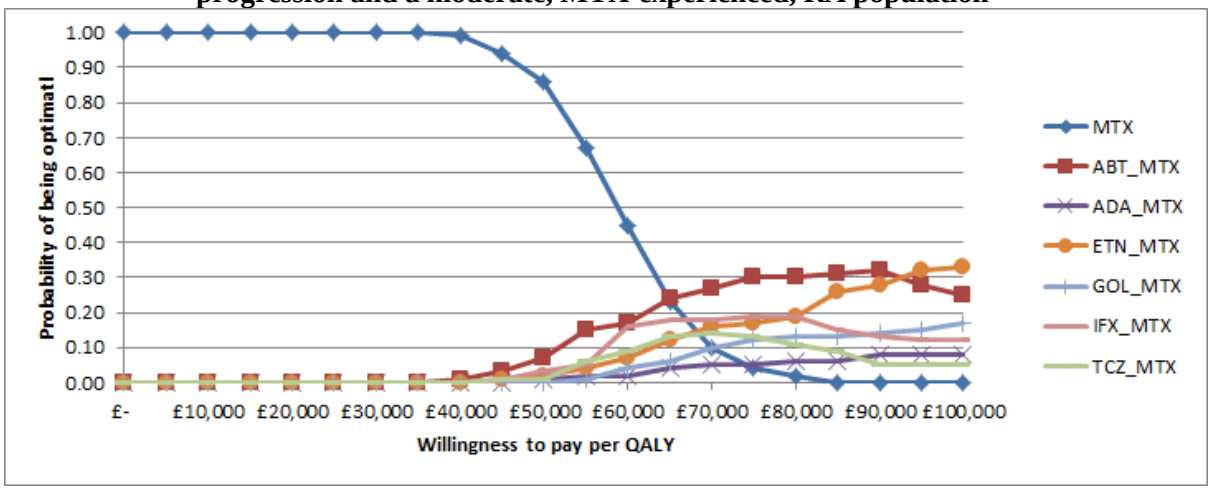
ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 237: Probabilistic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 61,767	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 59,400	£ 59,400
IFX_MTX	[redacted]	[redacted]	£ 60,425	Dominated
ADA_MTX	[redacted]	[redacted]	£ 63,763	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 62,229	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 61,960	£ 85,263
MTX	[redacted]	[redacted]	£ 58,837	£ 58,837

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 107: The CEAC when using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.6 EULAR response measure: Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

Table 238: Deterministic base case results using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 33,807	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 33,424	£ 33,424
ABT_MTX	[redacted]	[redacted]	£ 33,666	£ 49,138
ADA_MTX	[redacted]	[redacted]	£ 36,226	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 36,039	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 36,400	£ 69,450

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £33,000 to £37,000

Table 239: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 31,310	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 31,247	£ 31,247
IFX_MTX	[redacted]	[redacted]	£ 32,116	Dominated
ADA_MTX	[redacted]	[redacted]	£ 33,899	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 33,839	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 34,153	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 33,927	£ 68,887

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 240: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 32,714	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 32,691	£ 32,691
IFX_MTX	[redacted]	[redacted]	£ 33,227	Dominated
ADA_MTX	[redacted]	[redacted]	£ 34,925	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 34,614	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 35,159	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 34,257	£ 43,270

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 241: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABT_MTX	[redacted]	[redacted]	£ 33,212	£ 33,212
TCZ_MTX	[redacted]	[redacted]	£ 34,263	Dominated
IFX_MTX	[redacted]	[redacted]	£ 34,544	Dominated
ADA_MTX	[redacted]	[redacted]	£ 37,022	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 36,194	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 36,975	£ 94,201

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 242: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 20,993	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 19,902	£ 19,902
IFX_MTX	[redacted]	[redacted]	£ 20,346	Dominated
ADA_MTX	[redacted]	[redacted]	£ 21,803	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 21,723	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 22,096	£ 53,795

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 243: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 34,847	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 34,439	£ 34,439
ABT_MTX	[redacted]	[redacted]	£ 34,667	£ 49,138
ADA_MTX	[redacted]	[redacted]	£ 37,222	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 37,006	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 37,339	£ 69,450

ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 244: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	£ 40,024	£ 37,292
ABT_MTX	[redacted]	[redacted]	£ 41,329	£ 54,109
IFX_MTX	[redacted]	[redacted]	£ 44,316	Dominated
TCZ_MTX	[redacted]	[redacted]	£ 44,701	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 45,169	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 45,238	£ 87,583
ETN_MTX	[redacted]	[redacted]	£ 40,024	£ 37,292

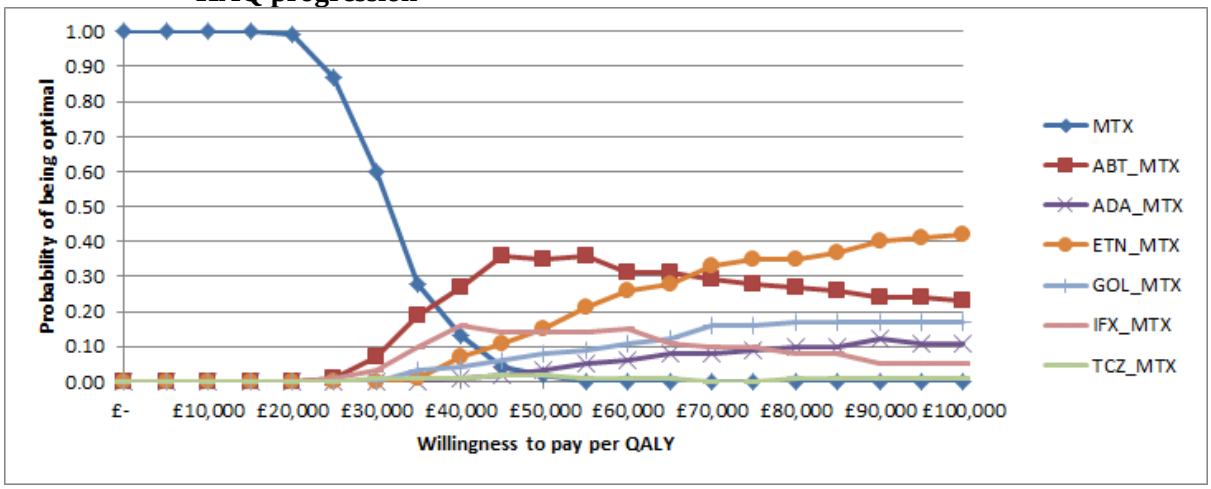
ABT iv – abatacept intravenous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 245: Probabilistic base case results using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
TCZ_MTX	[redacted]	[redacted]	£ 33,831	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 31,708	£ 31,708
IFX_MTX	[redacted]	[redacted]	£ 32,139	Dominated
ADA_MTX	[redacted]	[redacted]	£ 34,303	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 33,961	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 34,379	£ 64,825

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 108: The CEAC using EULAR data directly and assuming linear CDMARD HAQ progression



The CEAC shows only the probability of being optimal and inferences regarding relative cost-effectiveness shown be made with caution. It is seen that at a willingness to pay of £30,000 per QALY that the MTX strategy has the highest probability of being optimal.

6.3.22.7 ACR response measure: ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

Table 246: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 58,671	£ 58,671
TCZ_MTX	[redacted]	[redacted]	£ 58,742	Dominated
ABT_MTX	[redacted]	[redacted]	£ 58,909	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 61,311	£ 60,521
ADA_MTX	[redacted]	[redacted]	£ 63,513	Dominated
GOL_MTX	[redacted]	[redacted]	£ 63,645	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 62,007	Ext Dominated

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £58,000 to £64,000

Table 247: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 59,029	£ 59,029
TCZ_MTX	[redacted]	[redacted]	£ 61,640	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 59,068	£ 59,346
IFX_MTX	[redacted]	[redacted]	£ 60,143	Dominated
ADA_MTX	[redacted]	[redacted]	£ 62,581	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 62,216	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 62,731	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 60,703	£ 68,887

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 248: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 63,297	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 61,414	£ 61,414
TCZ_MTX	[redacted]	[redacted]	£ 64,727	Dominated
IFX_MTX	[redacted]	[redacted]	£ 65,729	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 64,988	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 67,169	Dominated
ETN_MTX	[redacted]	[redacted]	£ 65,950	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 63,397	£ 73,578

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 249: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 62,472	Ext Dominated
TCZ_MTX	[redacted]	[redacted]	£ 62,901	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 60,110	£ 60,110
IFX_MTX	[redacted]	[redacted]	£ 66,159	Dominated
GOL_MTX	[redacted]	[redacted]	£ 67,917	Dominated
ADA_MTX	[redacted]	[redacted]	£ 67,106	Dominated
ETN_MTX	[redacted]	[redacted]	£ 64,944	£ 143,192
MTX	[redacted]	[redacted]	£ 62,472	Ext Dominated

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 250: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 42,284	£ 42,284
IFX_MTX	[redacted]	[redacted]	£ 42,352	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 42,824	£ 46,501
TCZ_MTX	[redacted]	[redacted]	£ 47,019	Dominated
ADA_MTX	[redacted]	[redacted]	£ 45,051	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 44,991	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 45,148	£ 70,999
MTX	[redacted]	[redacted]	£ 42,284	£ 42,284

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 251: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 60,700	Ext Dominated
TCZ_MTX	[redacted]	[redacted]	£ 60,772	Dominated
ABT_MTX	[redacted]	[redacted]	£ 60,677	£ 60,677
IFX_MTX	[redacted]	[redacted]	£ 63,126	Dominated
ADA_MTX	[redacted]	[redacted]	£ 65,270	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 65,379	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 63,630	£ 91,315

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 252: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 67,146	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 65,431	£ 65,431
TCZ_MTX	[redacted]	[redacted]	£ 67,465	Dominated
IFX_MTX	[redacted]	[redacted]	£ 68,472	Dominated
ADA_MTX	[redacted]	[redacted]	£ 70,607	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 70,091	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 68,042	£ 85,227

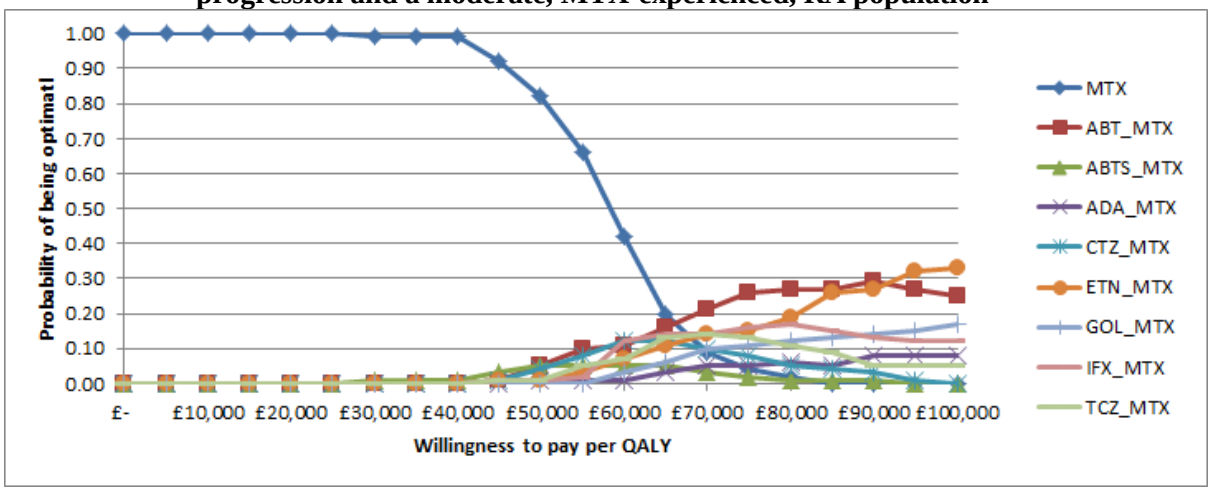
ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 253: Probabilistic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 58,837	£ 58,837
CTZ_MTX	[redacted]	[redacted]	£ 59,026	Dominated
TCZ_MTX	[redacted]	[redacted]	£ 61,767	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 59,400	£ 63,314
IFX_MTX	[redacted]	[redacted]	£ 60,425	Dominated
ADA_MTX	[redacted]	[redacted]	£ 63,763	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 62,229	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 61,960	£ 85,263
MTX	[redacted]	[redacted]	£ 58,837	£ 58,837

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 109: The CEAC when using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.8 ACR response measure: Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

Table 254: Deterministic base case results using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 31,888	£ 31,888
TCZ_MTX	[redacted]	[redacted]	£ 33,807	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 33,424	£ 48,266
ABT_MTX	[redacted]	[redacted]	£ 33,666	£ 49,138
ADA_MTX	[redacted]	[redacted]	£ 36,226	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 36,039	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 36,400	£ 69,450

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £31,000 to £38,000

Table 255: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 30,250	£ 26,830
TCZ_MTX	[redacted]	[redacted]	£ 31,310	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 31,247	£ 59,346
IFX_MTX	[redacted]	[redacted]	£ 32,116	Dominated
ADA_MTX	[redacted]	[redacted]	£ 33,899	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 33,839	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 34,153	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 33,927	£ 68,887

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 256: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 31,429	£ 31,429
TCZ_MTX	[redacted]	[redacted]	£ 32,714	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 32,691	£ 42,235
IFX_MTX	[redacted]	[redacted]	£ 33,227	Dominated
ADA_MTX	[redacted]	[redacted]	£ 34,925	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 34,614	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 35,159	Ext Dominated
CTZ_MTX	[redacted]	[redacted]	£ 34,257	£ 43,270

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 257: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 31,870	£ 31,870
ABT_MTX	[redacted]	[redacted]	£ 33,212	£ 42,196
TCZ_MTX	[redacted]	[redacted]	£ 34,263	Dominated
IFX_MTX	[redacted]	[redacted]	£ 34,544	Dominated
ADA_MTX	[redacted]	[redacted]	£ 37,022	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 36,194	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 36,975	£ 94,201

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 258: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 19,469	£ 19,469
TCZ_MTX	[redacted]	[redacted]	£ 20,993	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 19,902	£ 23,395
IFX_MTX	[redacted]	[redacted]	£ 20,346	Dominated
ADA_MTX	[redacted]	[redacted]	£ 21,803	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 21,723	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 22,096	£ 53,795

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 259: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 32,998	£ 32,998
TCZ_MTX	[redacted]	[redacted]	£ 34,847	Ext Dominated
IFX_MTX	[redacted]	[redacted]	£ 34,439	£ 48,266
ABT_MTX	[redacted]	[redacted]	£ 34,667	£ 49,138
ADA_MTX	[redacted]	[redacted]	£ 37,222	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 37,006	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 37,339	£ 69,450

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 260: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with the MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	£ 40,024	£ 37,292
ABTS_MTX	[redacted]	[redacted]	£ 41,380	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 41,329	£ 54,109
IFX_MTX	[redacted]	[redacted]	£ 44,316	Dominated
TCZ_MTX	[redacted]	[redacted]	£ 44,701	Ext Dominated
ADA_MTX	[redacted]	[redacted]	£ 45,169	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 45,238	£ 87,583
ETN_MTX	[redacted]	[redacted]	£ 40,024	£ 37,292

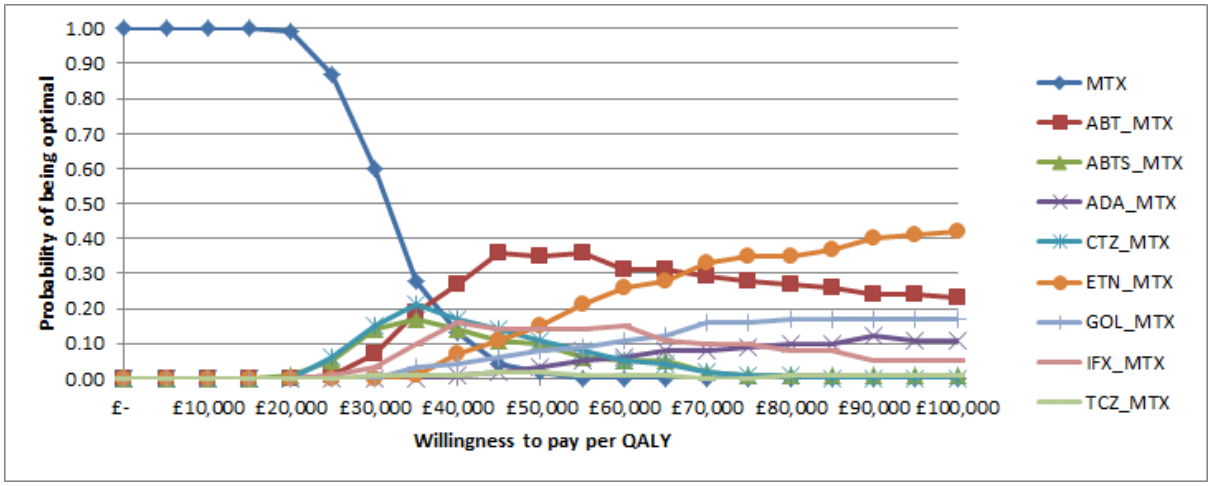
ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; CTZ – certolizumab pegol; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained; Ext - extendedly

Table 261: Probabilistic base case results using EULAR data directly – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]		
ABTS_MTX	[redacted]	[redacted]	£ 30,459	£ 41,944
TCZ_MTX	[redacted]	[redacted]	£ 33,831	Ext Dominated
ABT_MTX	[redacted]	[redacted]	£ 31,708	£ 42,213
IFX_MTX	[redacted]	[redacted]	£ 32,139	Dominated
ADA_MTX	[redacted]	[redacted]	£ 34,303	Ext Dominated
GOL_MTX	[redacted]	[redacted]	£ 33,961	Ext Dominated
ETN_MTX	[redacted]	[redacted]	£ 34,379	£ 64,825

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 110: The CEAC using EULAR data directly and assuming linear CDMARD HAQ progression



The CEAC shows only the probability of being optimal and inferences regarding relative cost-effectiveness shown be made with caution. It is seen however that in the willingness to pay region of £30,000 to £40,000 per QALY there are multiple bDMARDs with similar probabilities of being optimal.

6.3.22.9 EULAR response measure: ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

Table 262: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 68,756	£ 68,756
ETN	[redacted]	[redacted]	£ 73,532	£ 133,637
ADA	[redacted]	[redacted]	£ 75,403	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £68,000 to £76,000

Table 263: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 69,048	£ 69,048
ADA	[redacted]	[redacted]	£ 77,686	Ext Dominated
ETN	[redacted]	[redacted]	£ 76,623	£ 209,372

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 264: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 72,584	£ 72,584
ADA	[redacted]	[redacted]	£ 80,634	Ext Dominated
ETN	[redacted]	[redacted]	£ 79,831	£ 207,544

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 265: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 74,236	£ 74,236
ETN	[redacted]	[redacted]	£ 80,699	£ 185,842
ADA	[redacted]	[redacted]	£ 82,106	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 266: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 50,416	£ 50,416
ADA	[redacted]	[redacted]	£ 54,392	Ext Dominated
ETN	[redacted]	[redacted]	£ 54,219	£ 117,358

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 267: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 71,078	£ 71,078
ETN	[redacted]	[redacted]	£ 75,732	£ 133,637
ADA	[redacted]	[redacted]	£ 77,677	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 268: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 116,098	£ 116,098
ADA	[redacted]	[redacted]	£ 128,303	Ext Dominated
ETN	[redacted]	[redacted]	£ 125,659	£ 247,067

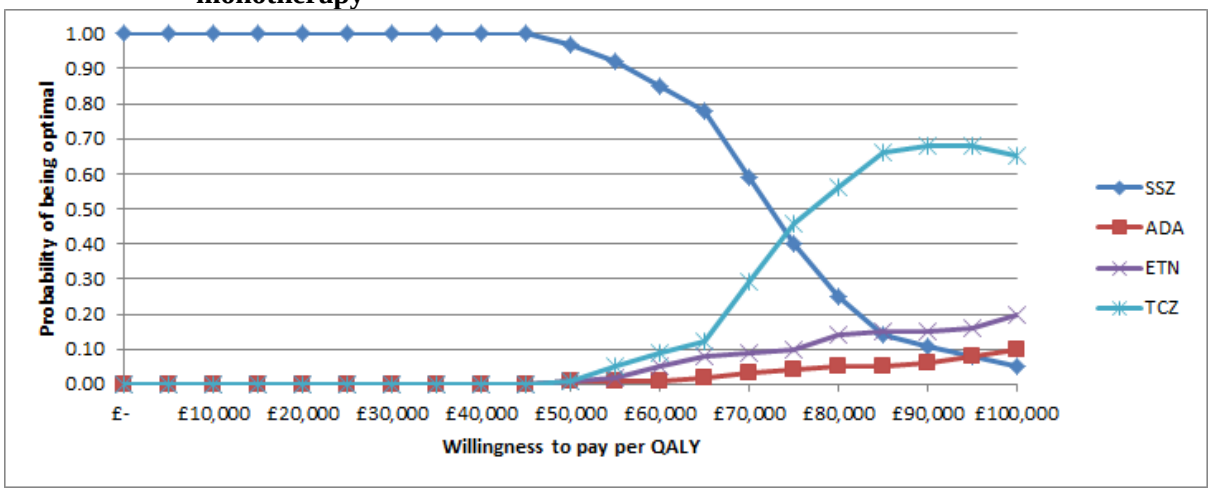
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 269: Probabilistic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 70,424	£ 70,424
ADA	[redacted]	[redacted]	£ 77,672	Ext Dominated
ETN	[redacted]	[redacted]	£ 76,129	£166,680

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 111: The CEAC when using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.10 EULAR response measure: Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

Table 270: Deterministic base case results using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 34,774	£ 34,774
ETN	[redacted]	[redacted]	£ 38,501	£ 106,692
ADA	[redacted]	[redacted]	£ 38,808	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £68,000 to £76,000

Table 271: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 33,668	Ext Dominated
ADA	[redacted]	[redacted]	£ 38,620	Ext Dominated
ETN	[redacted]	[redacted]	£ 38,334	£ 38,334

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 272: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 34,894	£ 34,894
ADA	[redacted]	[redacted]	£ 39,250	Ext Dominated
ETN	[redacted]	[redacted]	£ 39,003	£ 116,303

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 273: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 37,080	£ 37,080
ETN	[redacted]	[redacted]	£ 41,550	£ 146,591
ADA	[redacted]	[redacted]	£ 41,860	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 274: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 24,777	£ 24,777
ADA	[redacted]	[redacted]	£ 27,378	Ext Dominated
ETN	[redacted]	[redacted]	£ 27,259	£ 77,222

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 275: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 35,880	£ 35,880
ETN	[redacted]	[redacted]	£ 38,501	£106,692
ADA	[redacted]	[redacted]	£ 38,808	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 276: Deterministic results having used the relationship between HAQ and pain derived from LINEAR – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ			£ 66,620	£ 66,620
ADA			£ 75,535	Ext Dominated
ETN			£ 74,752	£230,503

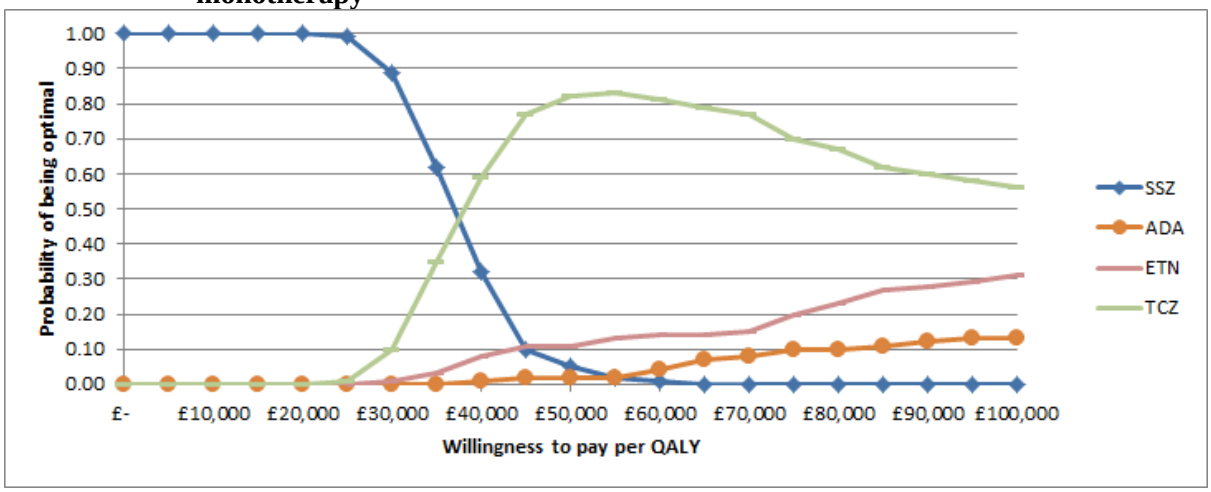
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 277: Probabilistic base case results using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ			£ 36,004	£ 36,004
ADA			£ 40,213	£ 29,262
ETN			£ 39,692	£ 4,006

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 112: The CEAC when using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has a high probability of being optimal.

6.3.22.11 ACR response measure: ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

Table 278: Deterministic base case results mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 63,288	£ 63,288
ETN	[redacted]	[redacted]	£ 65,556	£ 84,866
ADA	[redacted]	[redacted]	£ 65,729	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £63,000 to £66,000

Table 279: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 63,525	£ 63,525
ETN	[redacted]	[redacted]	£ 65,011	£ 75,676
ADA	[redacted]	[redacted]	£ 65,439	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 280: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 72,186	£ 72,186
ETN	[redacted]	[redacted]	£ 76,711	£125,145
ADA	[redacted]	[redacted]	£ 78,148	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 281: Deterministic results having included RCTs with potentially low prior MTX exposure using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 63,062	£ 63,062
ADA	[redacted]	[redacted]	£ 65,979	Ext Dominated
ETN	[redacted]	[redacted]	£ 65,572	£ 84,696

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 282: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 68,739	£ 68,739
ADA	[redacted]	[redacted]	£ 71,000	Ext Dominated
ETN	[redacted]	[redacted]	£ 70,294	£ 82,670

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 283: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 45,916	£ 45,916
ETN	[redacted]	[redacted]	£ 46,194	£ 48,079
ADA	[redacted]	[redacted]	£ 46,367	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 284: Deterministic results assuming 100-fold increased impact of adverse events and mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 65,376	£ 65,376
ETN	[redacted]	[redacted]	£ 67,444	£ 84,866
ADA	[redacted]	[redacted]	£ 67,619	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 285: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 107,818	£107,818
ADA	[redacted]	[redacted]	£ 111,491	Ext Dominated
ETN	[redacted]	[redacted]	£ 110,943	£134,488

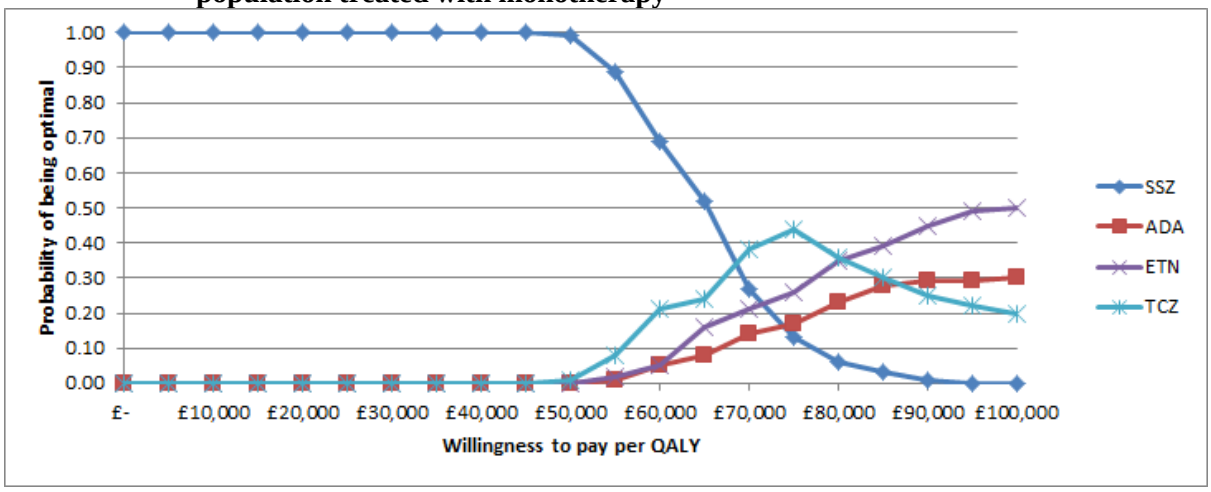
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 286: Probabilistic base case results mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 63,665	£ 63,665
ADA	[redacted]	[redacted]	£ 65,739	Ext Dominated
ETN	[redacted]	[redacted]	£ 65,341	£ 77,303

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 113: The CEAC when mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.12 ACR response measure: Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

Table 287: Deterministic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 33,661	£ 33,661
ETN	[redacted]	[redacted]	£ 36,531	Ext Dominated
ADA	[redacted]	[redacted]	£ 36,449	£ 69,531

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £33,000 to £37,000

Table 288: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 33,242	£ 33,242
ETN	[redacted]	[redacted]	£ 35,780	£ 62,520

ADA	[redacted]	[redacted]	£ 35,888	£377,351

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 289: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 32,025	£ 32,025
ETN	[redacted]	[redacted]	£ 35,214	£ 77,823
ADA	[redacted]	[redacted]	£ 35,883	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 290: Deterministic results having included RCTs with potentially low prior MTX exposure using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 107,818	£107,818
ADA	[redacted]	[redacted]	£ 111,491	Ext Dominated
ETN	[redacted]	[redacted]	£ 110,943	£134,488

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 291: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 35,976	£ 35,976
ADA	[redacted]	[redacted]	£ 38,582	Ext Dominated
ETN	[redacted]	[redacted]	£ 38,277	£ 62,708

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 292: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 23,592	£ 23,592
ETN	[redacted]	[redacted]	£ 24,928	£ 37,891
ADA	[redacted]	[redacted]	£ 25,084	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 293: Deterministic results assuming 100-fold increased impact of adverse events and mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 34,730	£ 34,730
ETN	[redacted]	[redacted]	£ 36,531	£ 72,189
ADA	[redacted]	[redacted]	£ 36,449	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 294: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 64,427	£ 64,427
ADA	[redacted]	[redacted]	£ 69,205	£122,081
ETN	[redacted]	[redacted]	£ 70,021	Dominated

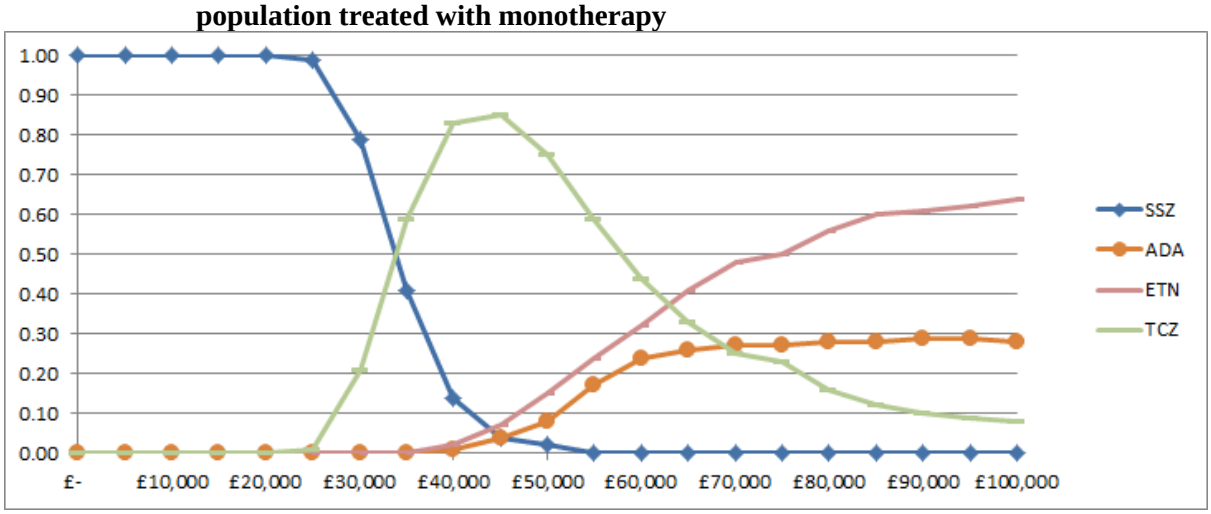
ADA – adalimumab; CTZ = certolizumab pegol; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 295: Probabilistic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 33,094	£ 33,094
ADA	[redacted]	[redacted]	£ 35,596	Ext Dominated
ETN	[redacted]	[redacted]	£ 35,532	£ 59,129

ADA – adalimumab; CTZ = certolizumab pegol; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 114: The CEAC when mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that both the MTX strategy and the tocilizimab strategy have reasonably high probabilities of being optimal.

6.3.22.13 EULAR response measure: ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

Table 296: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 72,081	£ 72,081
ADA	[redacted]	[redacted]	£ 76,354	Ext Dominated
ETN	[redacted]	[redacted]	£ 75,721	£117,580

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £72,000 to £77,000

Table 297: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 76,073	£ 76,073
ETN	[redacted]	[redacted]	£ 81,477	£118,913
ADA	[redacted]	[redacted]	£ 83,128	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 298: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 74,197	£ 74,197
ADA	[redacted]	[redacted]	£ 80,577	Ext Dominated
ETN	[redacted]	[redacted]	£ 79,990	£134,727

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 299: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 69,616	£ 69,616
ADA	[redacted]	[redacted]	£ 75,833	Ext Dominated
ETN	[redacted]	[redacted]	£ 74,969	£155,508

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 300: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 73,526	£ 73,526
ADA	[redacted]	[redacted]	£ 78,368	Ext Dominated
ETN	[redacted]	[redacted]	£ 77,643	£111,585

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 301: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 74,281	£ 74,281
ADA	[redacted]	[redacted]	£ 78,446	Ext Dominated
ETN	[redacted]	[redacted]	£ 77,779	£ 117,580

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 302: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 84,149	£ 84,149
ADA	[redacted]	[redacted]	£ 97,839	Ext Dominated
ETN	[redacted]	[redacted]	£ 94,973	£ 327,677

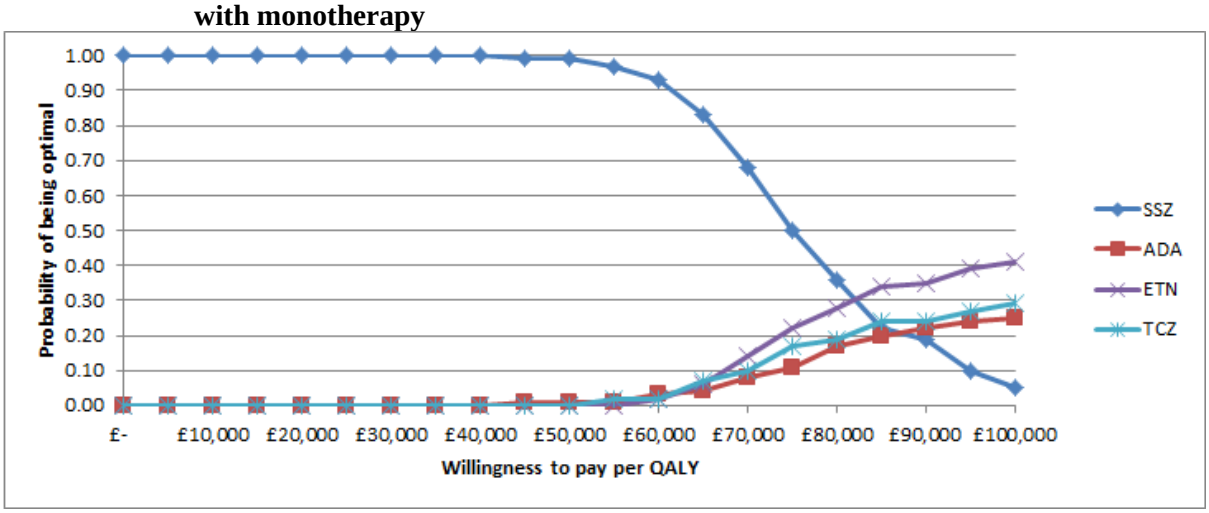
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 303: Probabilistic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 72,115	£ 72,115
ETN	[redacted]	[redacted]	£ 76,361	£131,694
ADA	[redacted]	[redacted]	£ 77,666	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 115: The CEAC when using EULAR data directly – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.14 EULAR response measure: Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

Table 304: Deterministic base case results using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 34,021	£ 34,021
ADA	[redacted]	[redacted]	£ 37,286	Ext Dominated
ETN	[redacted]	[redacted]	£ 36,863	£ 79,795

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £34,000 to £38,000

Table 305: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 34,250	£ 34,250
ETN	[redacted]	[redacted]	£ 38,595	£ 81,811
ADA	[redacted]	[redacted]	£ 39,254	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 306: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 33,706	£ 33,706
ADA	[redacted]	[redacted]	£ 36,089	Ext Dominated
ETN	[redacted]	[redacted]	£ 35,598	£ 54,844

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 307: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 34,829	£ 34,829
ADA	[redacted]	[redacted]	£ 38,567	Ext Dominated
ETN	[redacted]	[redacted]	£ 38,236	£ 97,385

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 308: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 34,946	£ 34,946
ADA	[redacted]	[redacted]	£ 38,031	Ext Dominated
ETN	[redacted]	[redacted]	£ 37,887	£ 68,116

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 309: Deterministic results assuming 100-fold increased impact of adverse events and using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 34,978	£ 34,978
ADA	[redacted]	[redacted]	£ 38,221	Ext Dominated
ETN	[redacted]	[redacted]	£ 37,775	£ 79,795

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 310: Deterministic results having used the relationship between HAQ and pain derived from LINEAR – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ			£ 48,718	£ 48,718
ADA			£ 55,370	Ext Dominated
ETN			£ 55,310	£172,621

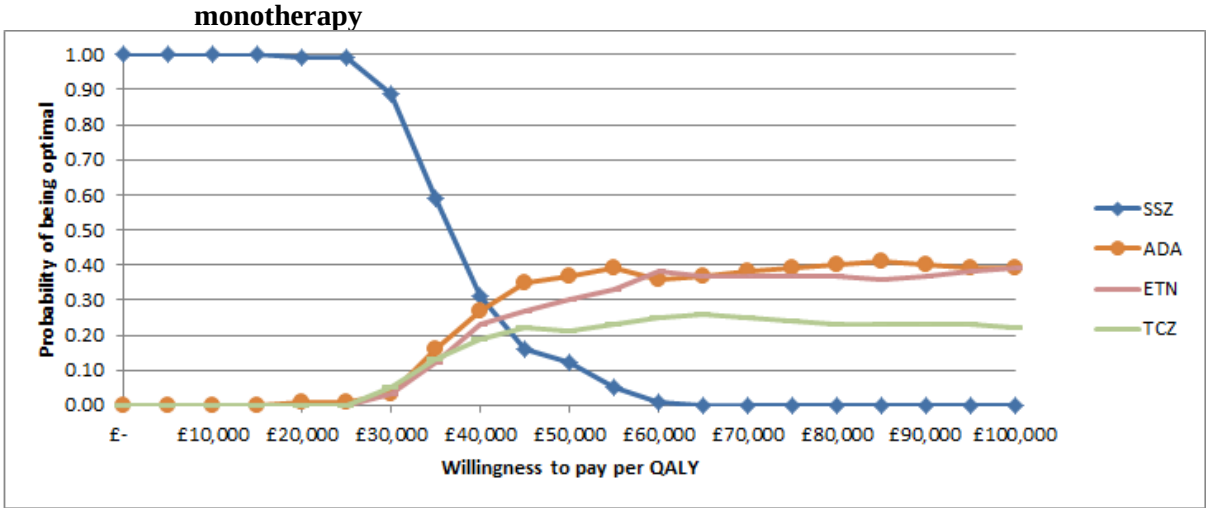
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 311: Probabilistic base case results using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ			£ 34,536	£ 72,115
ETN			£ 37,664	£131,694
ADA			£ 37,894	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 116: The CEAC when using EULAR data directly – LINEAR cDMARD HAQ progression and a severe, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has a high probability of being optimal.

6.3.22.15 ACR response measure: ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

Table 312: Deterministic base case results mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 67,267	£ 67,267
ADA	[redacted]	[redacted]	£ 70,006	Ext Dominated
ETN	[redacted]	[redacted]	£ 69,588	£ 91,218

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £67,000 to £77,000

Table 313: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 66,514	£ 66,514
ETN	[redacted]	[redacted]	£ 69,660	£102,006
ADA	[redacted]	[redacted]	£ 70,721	£249,910

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 314: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 80,530	£ 80,530
ETN	[redacted]	[redacted]	£ 83,545	£114,942
ADA	[redacted]	[redacted]	£ 86,202	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 315: Deterministic results having included RCTs with potentially low prior MTX exposure using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 69,514	£ 69,514
ADA	[redacted]	[redacted]	£ 69,990	£ 72,552
ETN	[redacted]	[redacted]	£ 71,434	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 316: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 68,718	£ 68,718
ETN	[redacted]	[redacted]	£ 69,604	Ext Dominated
ADA	[redacted]	[redacted]	£ 68,256	£ 65,232

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 317: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 48,759	£ 48,759
ADA	[redacted]	[redacted]	£ 49,974	Ext Dominated
ETN	[redacted]	[redacted]	£ 49,951	£ 64,398

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 318: Deterministic results assuming 100-fold increased impact of adverse events and mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 69,194	£ 69,194
ADA	[redacted]	[redacted]	£ 71,797	£100,672
ETN	[redacted]	[redacted]	£ 71,347	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 319: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 80,179	£ 80,179
ETN	[redacted]	[redacted]	£ 80,310	£ 81,132
ADA	[redacted]	[redacted]	£ 81,821	Dominated

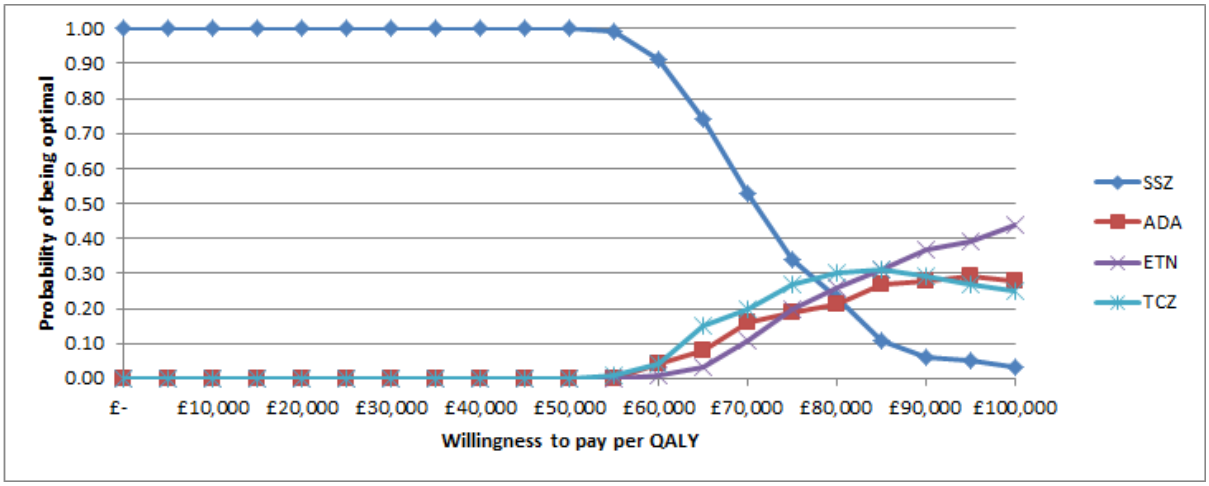
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 320: Probabilistic base case results mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 80,418	£ 71,499
ADA	[redacted]	[redacted]	£ 73,517	Ext Dominated
ETN	[redacted]	[redacted]	£ 72,684	£ 81,187

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 117: The CEAC when mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has a very high probability of being optimal.

6.3.22.16 ACR response measure: Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

Table 321: Deterministic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ			£ 33,992	£ 33,992
ADA	[redacted]	[redacted]	£ 36,114	Ext Dominated
ETN			£ 35,804	£ 56,284

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £33,000 to £37,000

Table 322: Deterministic results having included RCTs with a small proportion of previous bDMARD use (with adequate prior MTX exposure) mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 33,758	£ 33,758
ETN	[redacted]	[redacted]	£ 36,740	£ 84,334
ADA	[redacted]	[redacted]	£ 37,676	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 323: Deterministic results having included RCTs with a small proportion of previous bDMARD use (irrespective of prior MTX exposure) mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 32,935	£ 32,935
ETN	[redacted]	[redacted]	£ 34,967	£ 60,299
ADA	[redacted]	[redacted]	£ 35,316	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 324: Deterministic results having included RCTs with potentially low prior MTX exposure using ACR data mapped to EULAR data – ERAS cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 32,676	£ 32,676
ADA	[redacted]	[redacted]	£ 35,732	£ 62,480
ETN	[redacted]	[redacted]	£ 35,805	£378,975

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 325: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 36,481	£ 36,481
ETN	[redacted]	[redacted]	£ 37,717	Ext Dominated
ADA	[redacted]	[redacted]	£ 37,659	£ 48,158

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 326: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 23,622	£ 23,622
ADA	[redacted]	[redacted]	£ 24,588	£ 36,066
ETN	[redacted]	[redacted]	£ 24,793	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 327: Deterministic results assuming 100-fold increased impact of adverse events and mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 33,992	£ 33,992
ADA	[redacted]	[redacted]	£ 36,114	Ext Dominated
ETN	[redacted]	[redacted]	£ 35,804	£ 56,284

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 328: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 47,980	£ 47,980
ETN	[redacted]	[redacted]	£ 50,078	£ 66,929
ADA	[redacted]	[redacted]	£ 51,404	Dominated

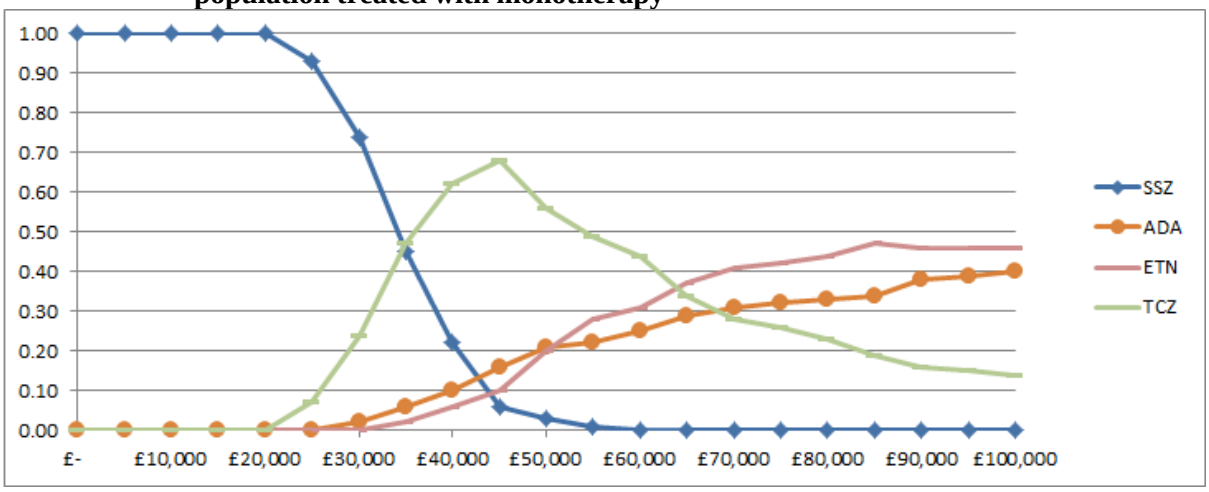
ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 329: Probabilistic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 47,980	£ 47,980
ETN	[redacted]	[redacted]	£ 50,078	£ 66,929
ADA	[redacted]	[redacted]	£ 51,404	Dominated

ADA – adalimumab; ETN – etanercept; SSZ = sulfasalazine; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Figure 118: The CEAC when mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a moderate, MTX-experienced, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX strategy has the highest probability of being optimal followed by the tocilizumab strategy.

6.3.22.17 Response measure ACR: ERAS cDMARD HAQ progression and a severe, MTX-naïve, RA population treated with monotherapy

Table 330: Deterministic base case results mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

Strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 63,251	£ 63,251
ADA	[redacted]	[redacted]	£ 97,667	£ 419,244

CPQ – cost per QALY gained.

Table 331: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 61,110	£ 61,110
ADA	[redacted]	[redacted]	£ 82,753	£ 169,246

CPQ – cost per QALY gained.

Table 332: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 38,696	£ 38,696
ADA	[redacted]	[redacted]	£ 62,685	£ 253,953

CPQ – cost per QALY gained.

Table 333: Deterministic results assuming 100-fold increased impact of adverse events and mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 65,719	£ 65,719

ADA	[redacted]	[redacted]	£ 100,283	£ 419,244

CPQ – cost per QALY gained. Ext - extendedly

Table 334: Deterministic results having used the relationship between HAQ and pain derived from ERAS – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 70,070	£ 70,070
ADA	[redacted]	[redacted]	£ 118,232	£ 2,980,632

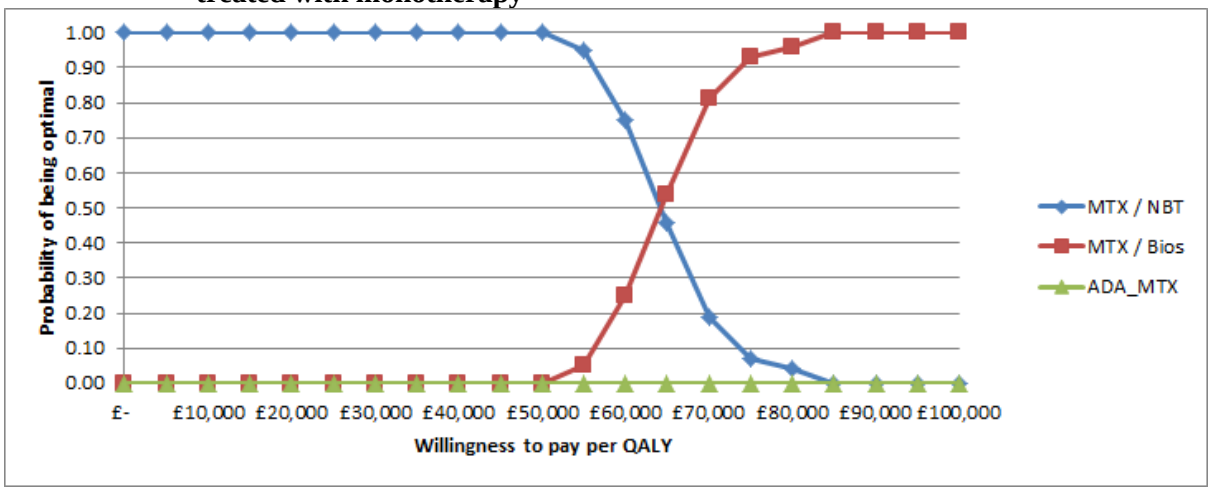
CPQ – cost per QALY gained.

Table 335: Probabilistic base case results mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

Strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 63,904	£ 63,904
ADA	[redacted]	[redacted]	£ 98,814	£ 482,985

CPQ – cost per QALY gained.

Figure 119: The CEAC when mapping EULAR data from ACR data – ERAS cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX / NBT strategy has a very high probability of being optimal.

6.3.22.18 Response measure ACR: Linear cDMARD HAQ progression and a severe, MTX-naïve, RA population treated with monotherapy

Table 336: Deterministic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

Strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 32,312	£ 32,312
ADA	[redacted]	[redacted]	£ 43,620	£ 102,679

CPQ – cost per QALY gained.

Table 337: Deterministic results having used the mapping of HAQ to utility from Malottki et al rather than Hernandez et al mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 33,088	£ 33,088
ADA	[redacted]	[redacted]	£ 44,735	£ 106,700

CPQ – cost per QALY gained.

Table 338: Deterministic results having used discount rates of 6% per annum for costs and 1.5% per annum for QALYs and mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 18,360	£ 11,980
ADA	[redacted]	[redacted]	£ 26,707	£ 71,636

CPQ – cost per QALY gained.

Table 339: Deterministic results assuming 100-fold increased impact of adverse events and mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 33,291	£ 33,291
ADA	[redacted]	[redacted]	£ 44,498	£ 102,679

CPQ – cost per QALY gained. Ext - extendedly

Table 340: Deterministic results having used the relationship between HAQ and pain derived from ERAS – Linear cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 18,360	£ 18,360
ADA	[redacted]	[redacted]	£ 26,707	£ 71,636

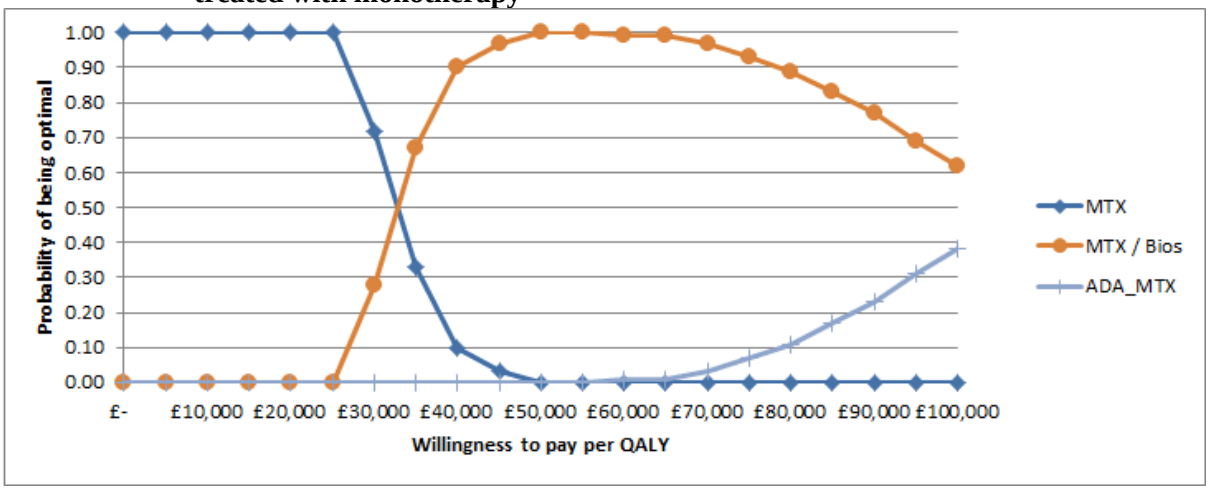
CPQ – cost per QALY gained.

Table 341: Probabilistic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy

Strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX / NBT	[redacted]	[redacted]		
MTX / Bios	[redacted]	[redacted]	£ 32,057	£ 32,057
ADA	[redacted]	[redacted]	£ 43,492	£ 104,052

CPQ – cost per QALY gained.

Figure 120: The CEAC when mapping EULAR data from ACR data – LINEAR cDMARD HAQ progression and a severe, MTX-naive, RA population treated with monotherapy



It is seen that at a willingness to pay of £30,000 that MTX / NBT strategy has a very high probability of being optimal.

6.4 Interpretation of the results

6.4.1 MTX-experienced RA patients

It is seen that the results are particularly sensitive to the assumptions made regarding the progression of HAQ whilst on cDMARDs.

The base case analyses undertaken by the Assessment Group estimates the HAQ progression whilst on cDMARDs to be that produced by a statistical analysis of the ERAS database, which contains a large number of patients diagnosed with RA with a 15-year follow up which results in ICERs for the bDMARDs consistently greater than £50,000 per QALY when compared to a cDMARD alone option, and often markedly higher. In contrast the manufacturers typically used a linear HAQ progression that has been used in previous NICE appraisals; when the Assessment Group used the same assumptions the ICERs were typically in the region of £30,000 - £40,000 per QALY.

The most appropriate HAQ progression to assume is discussed in section 6.3.14. The Assessment Group believes that the two analyses are likely to provide indications of the bounds on the ICERs however that the progression calculated from ERAS data is likely to be more plausible, although may underestimate HAQ progression as it may contain patients who would not receive bDMARDs.

Altering the discount rate to that used in the initial appraisals of bDMARDs (6% per annum for costs and 1.5% per annum for QALYs) noticeably reduces the ICERs; using the relationship between HAQ and pain from a different data source noticeable increase the ICERs. The ICERs for severe RA patients were typically lower than for moderate RA patients, although the difference was smaller when a linear HAQ progression was used.

The results between EULAR only data, and EULAR mapped from ACR were reasonably similar, which is reassuring given the wider evidence base reporting ACR data.

The ICERs for those patients who receive monotherapy are higher than for those who can be treated with MTX, increasing to approximately £74,000 per QALY using the ERAS HAQ progression and to £37,000 when using the linear HAQ progression. The Assessment Group believe that this is primarily due to the increased expenditure when rituximab cannot be provided, and a more expensive bDMARD (of similar efficacy) is used instead.

6.4.2 MTX-naïve RA patients

The ICERs associated with treating with bDMARDs prior to MTX is very high. The base case ICERs is greater than £400,000 per QALY; even assuming a linear progression of HAQ whilst on cDMARDs the values are in excess of £100,000 per QALY.

6.4.3 Discussion

6.4.3.1 Summary of Key results

Whilst there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in Population 1, infliximab + MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups; Intensive cDMARDs + prednisolone and adalimumab + MTX; etanercept, golimumab + MTX and step-up combination cDMARDs; adalimumab and cDMARDs.

Whilst there was uncertainty in, and overlap between the effects of treatment on EULAR for interventions in Population 2 and 3 in the main trials, etanercept + MTX and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: tocilizumab, golimumab + MTX, adalimumab + MTX, abatacept iv + MTX and grouped biologics; etanercept, infliximab + MTX, adalimumab and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly the same groupings, although

certolizumab pegol + MTX was associated with an even bigger response than etanercept + MTX and tocilizumab + MTX.

Whilst there was uncertainty in, and overlap between the effects of treatment on ACR for interventions in Population 2 and 3 in the main trials, etanercept + MTX, tocilizumab and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups:,etanercept, golimumab + MTX, abatacept sc + MTX, adalimumab + MTX, infliximab + MTX and abatacept iv + MTX; certolizumab pegol + MTX, intensive cDMARDs and adalimumab. The inclusion of the additional studies in which patients received prior biologics suggested that certolizumab pegol + MTX and etanercept + MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and adalimumab which are associated with even smaller response rates.

As described in section 6.2.3 the Assessment Group believes the ICERs for bDMARDs used in MTX-experienced patients with severe RA is credibly greater than £50,000 per QALY when compared to a cDMARD alone strategy. These values are marginally higher for moderate RA patients, higher for patients who cannot receive MTX, but greatly higher (£400,000 per QALY) when bDMARDs were used before cDMARDs.
These estimates are considereable lower if a different assumption, used in previous NICE appraisals were adopted (£30,000 - £35,000 for Populations 2 and 3 and £100,000 for Population 1). It is possible that the ICERs lie between these estimates but the Assessment Group believe that a 'true' value would be closer to the Assessment Group base case results.

The analyses have assumed that the discontinuation rule specified by NICE has been strictly adhered to; data from the BSRBR shows that this is not the case. If such non-adherence continues the ICERs will be considerably higher than those presented. Analysis of the impact has not been undertaken due to the possibility of back-calculation of commercial-in-confidence discounts offered through patient access schemes.

6.4.3.2 Generalisability of results

There is no reason to believe that the results detailed in this report are not generalizable to the English and Welsh populations.

6.4.3.3 Strengths and limitations of analysis

A strength of this report is that a systematic review of RCTs for bDMARDs in bDMARD-naïve patients has been conducted. The primary outcome measures are EULAR or ACR response at six-months and a formal NMA has been conducted to assess relative efficacy. Different analyses have been undertaken to assess the impact of including RCTs with a small proportion on patients with prior bDMARD use, and/or including RCTs when patients may have not had adequate prior MTX treatment.

A major strength of the analyses presented is that the Assessment Group has constructed a EULAR-based model that is much more appropriate to practice in England and Wales than previous ACR-based models. Estimates of ICERs for both EULAR data only, and when mapping ACR data to EULAR data indicate that the conclusions were not altered by restricting the selection of RCTs to only those that reported EULAR data.

An additional strength is that large observational databases were used to generate data on parameters such as HAQ change conditional on EULAR response and HAQ progression whilst on cDMARDs. This is preferable to data taken from relatively small RCTs of limited follow-up.

The model has known limitations. The plausible reduced efficacy of treatments when used subsequent to other treatments has not been formally incorporated. It is expected that this omissionwill favour bDMARDs. Additionally the effects of non-adherence to NICE guidelines (as shown in the BSRBR) have not formally been incorporated; it is expected that were this included then the ICERs for bDMARDs compared with cDMARDs would increase and disfavour bDMARDs.

Lost productivity has not been included in the model, which would favour bDMARDs if it were included.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Beyond potential impact on expenditure there is unlikely to be any major implications for the NHS as the interventions are largely subcutaneous and self-administered. Given the results presented in this report, it is unclear whether there will be an enlargement, a reduction, or no change in the expenditure on bDMARDs for patients with RA.

8. DISCUSSION

8.1 Statement of principle findings

Whilst there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in Population 1, infliximab + MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups; Intensive cDMARDs + prednisolone and adalimumab + MTX; etanercept, golimumab + MTX and step-up combination cDMARDs; adalimumab and cDMARDs.

Whilst there was uncertainty in, and overlap between the effects of treatment on EULAR for interventions in Population 2 and 3 in the main trials, etanercept + MTX and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: tocilizumab, golimumab + MTX, adalimumab + MTX, abatacept iv + MTX and grouped biologics; etanercept, infliximab + MTX, adalimumab and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly the same groupings, although certolizumab pegol + MTX was associated with an even bigger response than etanercept + MTX and tocilizumab + MTX.

Whilst there was uncertainty in, and overlap between the effects of treatment on ACR for interventions in Population 2 and 3 in the main trials, etanercept + MTX, tocilizumab and tocilizumab + MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups:,etanercept, golimumab + MTX, abatacept sc + MTX, adalimumab + MTX, infliximab + MTX and abatacept iv + MTX; certolizumab pegol + MTX, intensive cDMARDs and adalimumab. The inclusion of the additional studies in which patients received prior biologics suggested that certolizumab pegol + MTX and etanercept + MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and adalimumab which are associated with even smaller response rates.

The Assessment Group believes the ICERs for bDMARDs used in MTX-experienced patients with severe RA is credibly greater than £50,000 per QALY when compared to a cDMARD alone strategy. These values are marginally higher for moderate RA patients, higher for

patients who cannot receive MTX, but greatly higher (in excess of £100,000 per QALY) when bDMARDs were used before cDMARDs.

These estimates are considereable lower if a different assumption, used in previous NICE appraisals were adopted. It is possible that the ICERs lie between these estimates but the Assessment Group believe that a 'true' value would be closer to the Assessment Group base case results.

The analyses have assumed that the discontinuation rule specified by NICE has been strictly adhered to; data from the BSRBR shows that this is not the case. If such non-adherence continues the ICERs will be considerably higher than those presented. Analysis of the impact has not been undertaken due to the possibility of back-calculation of commercial-in-confidence discounts offered through patient access schemes.

8.2 Strengths and limitations of the assessment

A strength of this report is that a systematic review of RCTs for bDMARDs in bDMARD-naïve patients has been conducted. The primary outcome measures are EULAR or ACR response at six-months and a formal NMA has been conducted to assess relative efficacy. Different analyses have been undertaken to assess the impact of including RCTs with a small proportion on patients with prior bDMARD use, and/or including RCTs when patients may have not had adequate prior MTX treatment.

A major strength of the analyses presented is that the Assessment Group has constructed a EULAR-based model that is much more appropriate to practice in England and Wales than previous ACR-based models. Estimates of ICERs for both EULAR data only, and when mapping ACR data to EULAR data indicate that the conclusions were not altered by restricting the selection of RCTs to only those that reported EULAR data.

An additional strength is that large observational databases were used to generate data on parameters such as HAQ change conditional on EULAR response and HAQ progression whilst on cDMARDs. This is preferable to data taken from relatively small RCTs of limited follow-up.

The model has known limitations. The plausible reduced efficacy of treatments when used subsequent to other treatments has not been formally incorporated. It is expected that this omissionwill favour bDMARDs. Additionally the effects of non-adherence to NICE guidelines (as shown in the BSRBR) have not formally been incorporated; it is expected that were this included then the ICERs for bDMARDs compared with cDMARDs would increase and disfavour bDMARDs.

Lost productivity has not been included in the model, which would favour bDMARDs if it were included.

8.3 Uncertainties

The key uncertainty relating to the cost-effectiveness results is related to the HAQ progression whilst on cDMARDs. This has been shown to have a large influence on the results. The relationship between HAQ and pain can also greatly influence the ICER, as is currently uncertain with two large observational databases providing different estimated relationships.

9. CONCLUSIONS

9.1 Implications for service provision

The implications for service provision are unclear and would be dependent on the final guidance issued by NICE. The majority of interventions are administered subcutaneously by the patient or family member, although it is possible that requirements for infusions or for district nurse time are affected conditional on the final guidance

9.2 Suggested research priorities

In order to provide a more accurate estimate of the cost-effectiveness of bDMARDs the following research priorities are suggested by the Assessment Group. These aim to establish:

The evaluation of the long term HAQ trajectory whilst on cDMARDs
The relationship between HAQ and utility
The relationship between HAQ and hospital costs consumed
The relationship between HAQ and pain
The relative efficacy of bDMARDs assessed through head to head RCTs, although it is acknowledged that this is unlikely to occur due to the large scale, costly, RCTs that would be required.

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11. APPENDICES

Appendix 1 Protocol

See http://www.nice.org.uk/nicemedia/live/13754/61644/61644.pdf

Appendix 2: Table 342: table of excluded key studies with rationale for exclusion

Study	Rationale for exclusion
ADJUST Emery 2010[291]	Population DMARD-naive but moderate-severe (ABT)
AGREE Westhovens 2009[292]	Population: MTX naïve (not licensed for this population) (ABT)
ALLOW Kaine 2012[293]	Population: prior biologics (open-label run-in phase) (ABT)
ARRIVE Schiff 2009[294]	Population – previous use of anti-TNF therapy in all (ABT)
ATTAIN Genovese 2005[295]	Population – previous use of anti-TNF therapy in all (ABT)
ATTUNE Keystone 2012[296]	Study design: not RCT. Long-term extension of AIM and ATTAIN trials (ABT)
Burmester *et al.*, 2011 (TAMARA) (RM440) [297]	Not randomised controlled trial (single arm study) (TCZ)
Bykerk *et al.*, 2012 (RM24920) (ACT-SURE)[298]	Not randomised controlled trial (TCZ)
C87014 Choy 2012[299]	Intervention (not licensed dose) (CTZ)
CanACT Haraoui 2011 [300]	Not randomised controlled trial (ADA)
Chen 2006 RefID24610 [301]	Study investigating serum levels of anti-cyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor - excluded outcomes. (ETN)
Chen, 2009 RefID24609 [302]	Participants on MTX, unclear if had inadequate response, 12 week study, n=47 (ADA)
Choy 2002[303]	Intervention: not licensed dose (CTZ)
Choy *et al.*, 2002 (RM1301) [304]	Not in line with licensed indications
DART Moots 2011 [305]	Not randomised controlled trial (ADA, ETN, IFX)
Doseflex Furst 2012[306]	Population: prior biologics (open-label run-in) (CTZ)
Elliott *et al.*, 1994 (RM24634) [307]	Not in line with licensed indications (IFX)
Emery *et al.*, 2008 (RM24637) (RADIATE) [229]	Biologic-experienced population (outside appraisal scope) (TCZ)
FAST4WARD Fleischmann 2009[193]	Intervention: not licensed dose (CTZ)
Fleischmann 2012 RefID24648 [308]	Approximately 10% participants had prior biologics, fewer than 22 weeks of ADA treatment (10 weeks ADA then switch to

	TOF), so not included as additional evidence
Furst *et al.*, 2007 (RM24654) OPPOSITE [309]	Biologic-experienced population (outside appraisal scope) (IFX)
Genovese *et al.* 2012 [146]	Pooled data excluded
Genovese, the 20000223 study group 2004, RefID24661 [310]	Comparators unlicensed as ETN in combination with anakinra
Hall & Fleischmann, 2010 (RM10619) [311]	Insufficient details on data analyses and no useable pre-withdrawal data (TCZ)
HIKARI (NCT00791921) Yamamoto 2011[312]	Study design: no separate 6 month data for those with concomitant cDMARDs and monotherapy (CTZ)
Ingham *et al.*, 2012 (RESTART) (RM33192) [313]	All patients received IFX prior to randomisation to range of IFX doses (not comparable with other trial populations at baseline) (IFX)
Johnsen 2006 RefID 24682 [314]	Comparator unlicensed dose (ETN)
Kaufmann *et al.*, 2011 (RM24915) [315]	Not randomised controlled trial (TCZ)
Kavanaugh *et al.*, 2000 (RM24689) [316]	Not in line with licensed indications (IFX)
Kellner et al., 2011 (RM24916) [317]	Pre-treatment with biologics (TCZ)
Keystone, 2004 RefID24702 [318]	Can't distinguish results between monotherapy and combination therapy, half participants in each of three treatment arms given MTX, half not, 8week RCT stage of 16week study (ETN)
Khraishi *et al.*, 2011 [146]	Pooled data excluded (TCZ)
Kume *et al.*, 2011 (RM18240) [319]	All had prior biologics (TCZ)
Kume *et al.*, 2011 (RM24917) [320]	No useable scope outcome data (TCZ)
Leirisalo-Repo *et al.*, 2013 (NEO-RACo) (RM37795) [321]	Dosing interval in induction phase not in line with licensed indications (IFX)
Lim *et al.*, 2012 (RM24728) [322]	Insufficient description of statistical analyses in conference abstract to permit critical appraisal and handling of data (TCZ)
Lisbona 2008 RefID635 [323] and 2010 RefID 324 [324]	Treatment of tendosynovitis in RA, mostly excluded outcomes, 6 week study (ETN)
Lorenz *et al.*, 1996 (RM1860) [325]	Not in line with licensed indications (IFX)
Lorenz *et al.*, 2000 (RM1531) [326]	Not in line with licensed indications (IFX)
Maini *et al.*, 1998 (RM24732) [327]	Not in line with licensed indications (IFX)
Maini *et al.*, 2006 (RM24734) (CHARISMA) [328]	Low levels of prior biologics and no ACR-EULAR response data at weeks 22-30 for NMA (week 16 data only) (TCZ)
Makashima *et al.*, 2010 (RM24923) [329]	Not randomised controlled trial (TCZ)
Marcora 2006 RefID24735 [330] Gwynedd Hospital	Treatment of cachexia (ETN)
Markatseli *et al.*, 2012 (RM18131) [331]	Not randomised controlled trial (TNF inhibitors)
Moreland 1997 RefID24743 [332]	Unlicensed dose (ETN)
Nishimoto, 2010 [146]	Pooled data excluded
Pavelka *et al.*, 2009 (RM442) [333]	All patients received prior biologics (IFX)

Perkins *et al.*, 1998 (RM1633) [334]	Not in line with licensed indications (IFX)
PRESERVE Smolen 2013 RefID30145 [192]	All participants on ETN, before randomisation
PRIZE (unpublished, MS from Pfizer [183] MS)	All participants on ETN, before randomisation
ReACT Bombardieri 2007 [335]	Not randomised controlled trial , prior biologics (ADA)
Roux, 2011 RefID24764 [336]	Comparator steroid only (ETN)
Smeets *et al.*, 2003 (RM1227) [337]	No scope outcomes
Smolen *et al.*, 2009 (RM24780) (GO-AFTER) [212]	Biologic-experienced population (outside appraisal scope) (GOL)
STREAM van Eijk 2012 RefID24815 [338]	Participants didn't have to have diagnosis of RA to be eligible for trial, DAS under 3.2 (ADA)
Takeuchi 2012[339]	Population: prior biologics (ABT)
Takeuchi *et al.*, 2009 (RISING) (RM416) [340]	All patients received IFX prior to randomisation to range of IFX doses (not comparable with other trial populations at baseline) (IFX)
Takeuchi *et al.*, 2012 (RM24870) (GO-MONO) [341]	Not in line with licensed indications (monotherapy) (GOL)
Tam *et al.*, 2012 (RM24872) [342]	Insufficient description of cDMARD treatment history (and no ACR/EULAR data at 22-30 weeks) (IFX)
TAME Greenwald 2011 [343]	Comparator rituximab
Taylor *et al.*, 2004 [344]	Not in line with licensed indications (IFX)
van de Putte, 2003 [345]	Unlicensed dose (ADA)
Van Vollenhoven *et al*., 2009 (RM17453) [346]	Pooled data excluded (TCZ)
Weinblatt 2008 [347]	Unlicensed dose (ETN), all prior inadequate response to etanercept
Weinblatt *et al.*, 2012 (RM24868) (ACT-STAR) [348]	High proportion of prior biologic use (outside appraisal scope) (TCZ)
Westhovens 2005[349]	Population: inadequate response to anti-TNF therapy (ABT)
Westhovens *et al.*, 2006 (RM935) [350]	Not in line with licensed indications (IFX)
Westhovens *et al.*, 2012 (RM24845) (GO-FURTHER) [351]	Unlicensed dose (i.v. administration) (GOL)
Yamanaka *et al.*, 2011 (RM24921) (REACTION) [352]	Not randomised controlled trial (TCZ)
Yazici *et al.*, 2012 (RM24850) (ROSE) [353]	High proportion of prior biologic use (outside appraisal scope) (TCZ)

Table 343: Quality assessment: summary of findings

Trial	Intervention	Pop	MTC (Y/N)	Was the method used to generate the allocation sequence to treatment groups adequate? (Y/N/U)	Was the allocation of treatment concealed adequately? (Y/N/U)	Were the treatment groups comparable at baseline? (Y/N/U/ NA)	Were patients and study personnel blinded to treatment? (Y/N/U)	Were participants analysed in their allocated treatment groups? (Y/N/U)	Were all randomised patients included in efficacy analyses? (Y/N/U/ mITT/NA)	Were all randomised patients included in safety analyses? (Y/N/U/ mITT/NA)	Were at least 80% of participants originally randomised included in the final analysis? (Y/N/U)	Free of evidence of selective reporting of outcomes? (Y/N/U)
Abe 2006	IFX	2/3	N	U	U	Y	Y	U	mITT	mITT	Y	U
ACT-RAY	TCZ	2/3	Y	Y	Y	Y	Y	Y	mITT	mITT	Y	N
ADACTA	ADA, TOC	2/3	Y	Y	Y	Y	Y	Y	mITT	mITT	Y	N
ADORE	ETN	2/3	N	U	U	U	N	Y	mITT	mITT	Y	U
AIM	ABT	2/3	Y	Y	Y	Y	Y	Y	mITT	mITT	Y	Y
AMPLE	ADA, ABT	2/3	Y	U	U	Y	N	Y	mITT	mITT	Y	Y
APPEAL	ETN	2/3	N	U	U	Y	N	Y	mITT	mITT	Y	N
ARMADA	ADA	2/3	Y	U	U	Y	Y	Y	Y	Y	Y	U
ASPIRE	IFX	1	N	Y	Y	Y	Y	Y	N	mITT	Y	U
ASSET	ABT	2/3	N	Y	Y	N	Y	Y	mITT	mITT	Y	N
ASSURE	ABT	2/3	N	U	U	Y	Y	Y	mITT	mITT	Y	N
ATTEST	IFX, ABT	2/3	Y	U	U	Y	Y	Y	mITT	mITT	U	N
ATTRACT	IFX	2/3	Y	Y	Y	N	Y	Y	U	Y	Y	U
AUGUST II	ADA	2/3	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Bejarano 2008	ADA	1	N	Y	Y	Y	Y	Y	Y	Y	Y	N
BeST	IFX	1	Y	Y	N	Y	N	Y	U	U	Y	U

Trial	Intervention	Pop	MTC (Y/N)	Was the method used to generate the allocation sequence to treatment groups adequate? (Y/N/U)	Was the allocation of treatment concealed adequately? (Y/N/U)	Were the treatment groups comparable at baseline? (Y/N/U/ NA)	Were patients and study personnel blinded to treatment? (Y/N/U)	Were participants analysed in their allocated treatment groups? (Y/N/U)	Were all randomised patients included in efficacy analyses? (Y/N/U/ mITT/NA)	Were all randomised patients included in safety analyses? (Y/N/U/ mITT/NA)	Were at least 80% of participants originally randomised included in the final analysis? (Y/N/U)	Free of evidence of selective reporting of outcomes? (Y/N/U)
CERTAIN	CTZ	2/3	Y	U	U	U	Y	Y	U	U	Y	Y
CHANGE	ADA	2/3	Y	U	U	Y	Y	Y	Y	Y	Y	U
COMET	ETN	1	N	Y	Y	Y	Y	Y	mITT	mITT	Y	Y
DE0Y9	ADA	2/3	Y	U	U	Y	Y	Y	Y	Y	Y	Y
DeFilippis 2006	ETN, IFX	2/3	Y	U	U	Y	N	Y	N	N	Y	U
Durez 2004	IFX	2/3	N	U	U	N	N	Y	U	U	U	U
Durez 2007	IFX	1	Y	U	U	N	U	U	U	U	Y	Y
ERA	ETN	1	Y	U	U	Y	Y	Y	mITT	mITT	Y	U
ETN Study 309	ETN	2/3	Y	U	U	Y	Y	Y	mITT	mITT	Y	Y
GO-BEFORE	GOL	1	Y	Y	Y	Y	Y	Y	Y	mITT	Y	N
GO-FORTH	GOL	2/3	Y	U	U	Y	Y	Y	mITT	mITT	Y	Y
GO-FORWARD	GOL	2/3	Y	Y	Y	Y	Y	Y	Y	mITT	Y	N
GUEPARD	ADA	1	N	U	U	Y	N	Y	mITT	Y	Y	U
HIT HARD	ADA	1	Y	U	U	N	Y	Y	mITT	mITT	Y	U
IDEA	IFX	1	N	U	U	U	U	U	U	NA	U	U
IIBCREATE	ETN	2/3	Y	U	U	Y	N	Y	Y	Y	Y	N
JESMR	ETN	2/3	Y	U	U	N	N	Y	mITT	mITT	Y	Y
Kay 2008	GOL	2/3	N	U	U	N	Y	Y	Y	mITT	Y	N
Kim 2007	ADA	2/3	Y	U	U	Y	Y	Y	mITT	Y	Y	U
Kume 20YY	ADA, ETN	1	N	U	U	Y	N	Y	N	NA	Y	N
Lan 2004	ETN	2/3	N	U	U	Y	Y	Y	mITT	mITT	Y	U

Trial	Intervention	Pop	MTC (Y/N)	Was the method used to generate the allocation sequence to treatment groups adequate? (Y/N/U)	Was the allocation of treatment concealed adequately? (Y/N/U)	Were the treatment groups comparable at baseline? (Y/N/U/ NA)	Were patients and study personnel blinded to treatment? (Y/N/U)	Were participants analysed in their allocated treatment groups? (Y/N/U)	Were all randomised patients included in efficacy analyses? (Y/N/U/ mITT/NA)	Were all randomised patients included in safety analyses? (Y/N/U/ mITT/NA)	Were at least 80% of participants originally randomised included in the final analysis? (Y/N/U)	Free of evidence of selective reporting of outcomes? (Y/N/U)
LARA	ETN	2/3	Y	U	U	Y	N	Y	mITT	Y	Y	U
MEASURE	TCZ	2/3	N	U	U	U	Y	U	U	NA	U	U
Moreland Y999	ETN	2/3	Y	Y	Y	Y	Y	Y	mITT	mITT	Y	U
Nishimoto 2004	TCZ	2/3	N	U	U	Y	Y	Y	Y	Y	Y	U
OPERA	ADA	1	N	Y	Y	Y	Y	Y	mITT	mITT	Y	U
OPTIMA	ADA	1	Y	Y	Y	Y	Y	Y	mITT	mITT	Y	Y
PREMIER	ADA	1	Y	U	U	N	Y	Y	mITT	mITT	Y	U
Quinn 2005	IFX	1	N	U	U	Y	Y	Y	U	U	Y	U
RACAT	ETN	2/3	Y	Y	Y	Y	Y	Y	N	N	Y	Y
REALISTIC	CTZ	2/3	N	Y	Y	Y	U	Y	Y	mITT	Y	N
RED-SEA	ADA, ETN	2/3	N	Y	N	Y	N	Y	mITT	mITT	Y	Y
SAMURAI	TCZ	2/3	Y	U	Y	Y	N	Y	mITT	mITT	Y	U
SATORI	TCZ	2/3	Y	Y	Y	Y	Y	Y	mITT	mITT	Y	N
STAR	ADA	2/3	Y	U	U	Y	Y	Y	mITT	mITT	Y	U
START	IFX	2/3	Y	U	U	Y	Y	Y	mITT	N	Y	U
Swefot	IFX	2/3	Y	Y	Y	Y	N	Y	Y	Y	Y	N
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOWARD	TCZ	2/3	Y	U	U	Y	Y	Y	mITT	mITT	Y	U
van de Putte 2004	ADA	2/3	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Wajdula 2000	ETN	2/3	N	U	U	Y	Y	U	U	U	Y	U

Trial	Intervention	Pop	MTC (Y/N)	Was the method used to generate the allocation sequence to treatment groups adequate? (Y/N/U)	Was the allocation of treatment concealed adequately? (Y/N/U)	Were the treatment groups comparable at baseline? (Y/N/U/ NA)	Were patients and study personnel blinded to treatment? (Y/N/U)	Were participants analysed in their allocated treatment groups? (Y/N/U)	Were all randomised patients included in efficacy analyses? (Y/N/U/ mITT/NA)	Were all randomised patients included in safety analyses? (Y/N/U/ mITT/NA)	Were at least 80% of participants originally randomised included in the final analysis? (Y/N/U)	Free of evidence of selective reporting of outcomes? (Y/N/U)
Weinblatt Y999	ETN	2/3	Y	U	U	Y	Y	Y	Y	Y	Y	U
Wong 2009	IFX	2/3	N	U	U	Y	Y	Y	U	NA	U	U
Zhang 2006	IFX	2/3	N	U	U	N	Y	U	U	U	U	U

Table 344: Trial characteristics: Population 1 head to head RCT

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract)
Kume 2011 [90]	RCT (open-label)	ADAmon (n=22 randomised)	NA	NR	24 weeks	Change in cardio-ankle vascular index (CAVI)	All patients with worsening disease activity (DAS28-ESR >5.1 or change from baseline of DAS28-ESR >1.at week 12 were allowed to leave the group, by clinican's judgement.	Japan	NR	Kume 2011 full text Kume *et al.*, 2011 (RM24724)
Kume 2011		ETNmon (n=21 randomised)	NA	NR						

Key:
ABT i.v. = abatacept ~10mg/kg intravenously on weeks 0, 2 and 4, and every 4 weeks thereafter
ABT s.c. = abatacept 125mg once per week subcutaneously, following an optional intravenous loading dose of ~10mg/kg based on weight range
ADA = adalimumab 40mg every other week subcutaneously
CTZ = subcutaneous certolizumab pegol 400mg at weeks 1, 2 and 4, then 200mg every other week
DMARDs = conventional DMARDs
ETN = etanercept 25mg twice a week subcutaneously
ETN50 = etanercept 50mg once a week subcutaneously
GOL = golimumab 50 mg every 4 weeks subcutaneously
HCQ = Hydroxychloroquine
IFX = infliximab 3 mg/kg intravenously at weeks 0, 2, 6 and every 8 weeks thereafter (with dose escalation permitted after week 12 if lack of response)
IQR = interquartile range
LEF = leflunomide
mon = monotherapy, without cDMARDs
MTX = methotrexate
PBO = placebo
RCT = randomised controlled trial

SSZ = Sulfasalazine
TCZ = tocilizumab 8 mg/kg intravenously every 4 weeks

Table 345: Trial characteristics: Population 1 biologics vs. DMARD(s) or PBO

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
Bejarano 2008[69]	multicentre, RCT	PBO+MTX n=73	MTX dosage increased from 7.5 to 25 mg/ week by week 12 in the presence of remaining synovitis	Folate was administered according to regionally agreed guidelines (5 mg 6 times/week). Stable doses of anti-inflammatory drugs, analgesics, and prednisolone (up to10 mg/day) were maintained in order for study treatment effect to be assessed without confounders. Swollen joints were permitted to be treated during the study with intra-articular injections of methylprednisolone (up to 80 mg over the course of the study).	56 weeks	job loss of any cause and/or imminent job loss at or after week 16	Rules for participant withdrawal included job loss, imminent job loss, and adverse events (at the discretion of the physician). Physicians could withdraw patients due to an unacceptably high disease activity	UK	Abbott Laboratories	Bejarano 2008[69] [69] (full article in peer-reviewed journal)
Bejarano 2008[69]		ADA+MTX n=75								
GUEPARD[83] a French acronym for GUe´ rir laPolyArthrite Rhumatoide De´butante (cure early RA),	RCT, prospective, unblinded	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28 n=32 treatment adjusted	12 weeks MTX 0.3 mg/kg/week, maximum of 20 mg/week, without escalating dose regimen	Patients were allowed to continue concomitant treatment with corticosteroids initiated before but not after inclusion (maximum daily dose of 10 mg of oral prednisone) and to	1 year	the proportion of patients in low disease activity at Week 12 for whom anti-TNF-was not introduced or reintroduced at 1 year.	step-up therapy part of intervention groups	France	Supported by a grant from the French Society of Rheumatology and the adalimumab treatment was provided free of charge by Abbott France	Soubrier 1999 [83](full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
Soubrier 1999 RefID24782		every 3 months on the basis DAS28 If the patient did not achieve a low disease activity (DAS28<or=3.2), the treating physician adjusted therapy by proceeding to the next step in the allocated treatment group initial monotherapy started with MTX (0.3 mg/kg/week, maximum of 20 mg/week, without escalating dose regimen). In the event of remission (DAS28<2.6 for at least 6 months), MTX was tapered (2.5 mg/month) to a maintenance dose of 7.5 mg/week. If disease activity flared after tapering of MTX, the initial dose of MTX was reintroduced. Subsequent steps for patients with an insufficient response at Week 12 or thereafter were MTX and ADA (40 mg every other	(then step-up)	take NSAIDs and simple analgesics. A single IA steroid injection was allowed during the trial. All patients received folic acid (20 mg 72 h after MTX therapy)						

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
		week), MTX and ADA (40 mg/week), MTX and etanercept (25 mg twice a week) and MTX and LEF.								
GUEPARD		Initial ADA+MTX ADA 40mg s.c. eow 12 weeks, then step-up therapy in both groups based on DAS28 n=33 treatment adjusted every 3 months on the basis DAS28 If the patient did not achieve a low disease activity (DAS28<or=3.2), the treating physician adjusted therapy by proceeding to the next step in the allocated treatment group If the DAS28 was <3.2 at Week 12, ADA was stopped. In the event of remission (DAS28<2.6 for at least 6 months), MTX was tapered (2.5 mg/month) to a	12 weeks MTX 0.3 mg/kg/week, maximum of 20 mg/week, without escalating dose regimen (then step-up)							

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
		maintenance dose of 7.5 mg/week. If disease activity flared after tapering of MTX, the initial dose of MTX was reintroduced. In the event of relapse, patients restarted ADA 40 mg every other week for 12 weeks. If the DAS28 was >3.2 after 12 weeks, ADA was stopped. In the event of inefficacy (DAS28>3.2 after 12 weeks of treatment), ADA was increased (40 mg/week) for 12 weeks. After 12 weeks of effective therapy, ADA was decreased (40 mg every other week) for 12 weeks and stopped if successful. In the event of failure on ADA 40 mg/week, etanercept (25 mg twice a week) was initiated for 12 weeks. If effective, etanercept was stopped and started again for 12 weeks if relapse occurred. If etanercept failed,								

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
		LEF was initiated. If the treatment was unsuccessful after the initial 12 weeks, the same regimen was applied according to the protocol indicated above.								
HIT HARD[84]	RCT	MTX + PBO (85 randomised)	15mg/week	Folic acid 10 mg/week, stable dose of ≤10 mg/day prednisone or equivalent permitted	24 weeks	DAS28 at week 48	No	Germany	German Federal Ministry of Education and Research (ADA provided by Abbott under unconditional scientific grant)	Detert 2013 [84] full paper
HIT HARD		ADA + PBO (87 randomised)	NA							
OPERA [97]	RCT	MTX + PBO + steroid (91 randomised)	Dose escalated from 7.5 mg/week at baseline to 15 mg/week at 1 month and 20 mg/week after 2 months (or highest tolerated dose)	Folic acid (5-10 mg/week) and oral calcium with vitamin D (1000 mg calcium + 800 IU vitamin D daily). Alendronate (70 mg/week) initiated at baseline and mild analgesics (but not NSAIDs, muscle relaxants or other analgesics) were permitted.	12 months	Proportion of patients in each group that had achieved low disease activity (DAS28CRP <3.at 12 months.	Treatment escalation – HCQ or SSZ given at 3 months if DAS28CRP ≥3.2 and ≥1 swollen joint or 4mg triamcinolone had been given monthly for 3 consecutive months. If low disease activity not achieved by 6 months patient treated as a non-responder, excluded and	Denmark	Abbott Laboratories, Denmark (who also provided free ADA & PBO). Triamcinolone supplied by Meda Pharmaceuticals, Denmark.	Horslev-Petersen [97] 2013 full paper

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
							open-label biologics (not ADA) prescribed.			
OPERA [97]		ADA + MTX + steroid (89 randomised)								
OPTIMA	RCT (Phase 4)	MTX + PBO (517 randomised)	Titrated to 20 mg/week by week 8	NSAIDs (79%), corticosteroids (46%)	26 weeks	Composite of DAS28(CRP) <3.2 at week 78 and no radiographic progression from baseline to week 78	No	North and South America, Europe, Africa, New Zealand and Australia	Abbott Laboratories	Kavanaugh 2012 [98] full paper Peterfy 2010 abstract (RM16535) Emery 2011 abstract (RM14751) Smolen 2010 abstract (RM24774)
OPTIMA		ADA + MTX (515 randomised)		NSAIDs (78%), corticosteroids (41%)						
PREMIER [99]	RCT	MTX + PBO (257 randomised)	7.5 mg/week for first 4 weeks, increased to 15 mg/week weeks 4-8 if tolerated and to 20 mg/week at week 9.	Folic acid, 5-10 mg/week	2 years	ACR50 response and mean change from baseline in mTSS	Dose escalation (frequency) of ADA or PBO for those not achieving ACR20 response at week 16 or later	Australia, Europe and North America	Abbott Laboratories	Breedveld 2006 full paper[99] Van der Heijde 2010 full text (RM7096) Emery 2009 full text (RM24640) Strand 2012 full text (RM24790)
PREMIER		ADA mon + PBO step up week 16 (274 randomised)	NA							
PREMIER		ADA + MTX step up week 16 (268 randomised)	7.5 mg/week for first 4 weeks, increased to 15							

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
			mg/week weeks 4-8 if tolerated and to 20 mg/week at week 9.							
COMET Combination of Methotrexate and Etanercept in Early Rheumatoid Arthritis NCT00195494 Emery 2008 RefID24638	prospective double blind multicentre RCT	MTX +PBO n=268 1st period comprised 2 randomised groups a) MTX monotherapy in year 1 followed by combination (ETN+MTX) treatment in year 2 n=90 at start of period 2 b) MTX monotherapy in year 1 followed by continued MTX monotherapy in year 2 n=99 at start of period 2	starting at 7·5 mg once a week. In patients with tender or swollen joints, the dose was titrated up over 8 weeks to a maximum of 20 mg a week	Stable doses of oral corticosteroids (≤10 mg per day of prednisone or an equivalent agent) or a single non-steroidal anti-inflammatory drug were permitted if started at least 4 weeks before baseline and kept constant throughout the first 24 weeks of the study.	52weeks	Coprimary endpoints were the proportion of patients achieving remission (DAS28 <2·6) at week 52 and the change in van der Heijde modified total Sharp score (mTSS; joint erosion score plus joint space narrowing score) from baseline to week 52	NR	Europe, Latin America, Asia, and Australia	Wyeth Research	Emery 2008 [73] (full article in peer-reviewed journal)
COMET		ETN+MTX n=274 1st period comprised 2 randomised groups a) combination etanercept plus MTX treatment in year 1 followed by continued combination	starting at 7·5 mg once a week. In patients with tender or swollen joints, the dose was titrated up over 8 weeks to a maximum of 20 mg a week							

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
		treatment in year 2 n=111 at start of period 2 b) combination treatment in year 1 followed by etanercept alone in year 2 n=111 at start of period 2								
ERA	RCT	MTX + PBO (217 randomised)	Initial dose of 7.5 mg/week escalated to 15mg/week at week 4 and 20 mg/week at week 8. One 5mg reduction permitted.	Folic acid (1 mg/day)	12 months	Overall response during the first 6 months	No	NR	Immunex	Bathon 2000 [77]full paper Bathon 2003 full text (RM24859) Kosinski 2002 full text (RM24711)
ERA, Bathon 2000 Multicentre		ETN + PBO (207 randomised)								
GO-BEFORE (EudraCT database no. 2004-003295-10)	RCT (Phase III, double-blind)	PBO + MTX (N=160)	19.1 (SD=2.7(week 23)	NSAIDs, other analgesics for RA, and oral corticosteroids (≤ 10 mg prednisone/day or equivalent) permitted if doses stable for ≥ 2 weeks before initiation of study agent and during treatment.	52 weeks	Co-primary endpoints: ACR50 response at week 24 Change from baseline in modified Sharp / van der Heijde score at week 52	No	Multicentre, multinational (90 sites across Europe/Australia/New Zealand (n=34), Asia (n=25), North American (n=2and Latin America (n=10)	Centocor Research and Development and Schering-Plough Research Institute)	Emery *et al.*, 2009 (RM24639) (full publication)[80] 136
GO-BEFORE		GOL 50 mg s.c. every 4 weeks + MTX (N=159)	19.2 (SD=2.35) (week 23)							
ASPIRE	RCT (Phase	PBO. + MTX (298	MTX started at	Oral corticosteroids	54 weeks	For	No	Multicentre,	Centocor	St Clair *et al.*,

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
(Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset)	3, double-blind)	randomised)	7.5 mg/wk and increased (2.5 mg/wk every 1-2 weeks) to 15 mg/wk by week 4 and 20 mg/wk by week 8. MTX dose could be adjusted in case of intolerance.	(≤ 10 mg/day prednisone or equivalent) and NSAIDs maintained at baseline doses. Other DMARDs not allowed during study.		radiographic progression of joint damage: change from baseline to week 54 in van der Heijde modification of total Sharp score. For physical function: change from baseline in HAQ scores averaged over weeks 30-54.		multinational (122 sites in North America and Europe)		2004 (full publication) (RM24613)[63]
ASPIRE		IFX i.v. 3 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter + MTX (373 randomised)								
BeST	RCT (Phase NR, open label)	Sequential monotherapy (126 randomised)	DAS-steered step-up strategies for all 4 treatment groups	Concomitant treatment with NSAIDs and i.a. injections with corticosteroids permitted.	3 years	HAQ and modified Sharp/van der Heijde score	No (DAS-steered step-up strategies for all 4 treatment groups)	Multicentre, Netherlands	Dutch College of Health Insurances Schering-Plough	Goekoop-Ruiterman *et al.*, 2005 (full publication (RM639) [70]
BeST		Step-up combination therapy (121 randomised)								
BeST		Initial combination therapy with prednisone (133 randomised)								
BeST		Initial combination therapy with IFX (128 randomised)								
Durez 2007	RCT (Phase	MTX (14	All patients	Patients receiving	12	Evaluation of	No	Belgium	Schering-Plough	Durez *et al.*,

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
(NCT00396747)	IV, single-blind)	randomised)	received MTX at dosage ranging from 7.5 mg/week (baseline) to 20 mg/wk (week 14).	NSAIDs required to be receiving stable doses (remaining unchanged during study). i.e. steroids not permitted. Introduction of oral glucocorticosteroids of other DMARDs not permitted.	months	MRI scores over time				2007 (full publication (RM2463[354]
Durez 2007		MTX + i.v. methyprednisolone (MP) 1 g at weeks 0, 2 and 6 and then every 8 weeks thereafter (15 randomised)								
Durez 2007		IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22, 30, 38, 46 +MTX (15 randomised)								
IDEA	RCT (Phase, NR, double-blind to week 26)	MP 250 mg i.v. at week 0, PBO i.v. at weeks 2, 6, 14, 22 + MTX Numbers randomised NR (112 patients included across both groups)	+ MTX 10 mg weekly increasing to 20 mg by week 6	NR	78 weeks	NR	Step-up from week 26 if DAS > 2.4 Other biologics permitted from week 26 (no further details) (data extracted to week 26)	Multicentre (no further details)	NR	Nam *et al.*, 2011 (conference abstract) (RM24747)
IDEA		IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22 + MTX (IFX dose modifications permitted according to DAS44 from week 26)								

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
		Numbers randomised NR (112 patients included across both groups)								
Quinn 2005	RCT	MTX + PBO (10 randomised)	7.5 mg/week with escalation up to 15 mg/week by week 14. Increments up to 25 mg/week titrated against evidence of active disease.	Folic acid 5mg/twice a week	54 weeks	Comparison of MRI-measured synovitis at week 14 between groups	No	NR	Arthritis Research Campaign	Quinn 2005 full paper [100] Haugeberg 2009 full paper 24927 Bejarano 2010 full paper 286
Quinn 2005		IFX 3mg/kg + MTX (10 randomised)								

Table 346: Trial characteristics: Populations 2/3 head to head RCTs

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
ATTEST[66] (NCT00095147)	RCT (Phase III, double blind)	PBO+MTX (with blinded crossover to ABT at day 198) (110 randomised)	No MTX dose adjustments permitted except due to adverse events. MTX dose could be altered (to less than 25 mg/wk) between days 198-365	Permitted days 1-197: oral corticosteroids (≤10 mg/day prednisone or equivalent) (stable ≥ 25 / 28 days prior to randomisation), and/or stable NSAIDs and analgesics. Days 198-365 dose of oral corticosteroids could be modified (≤10 mg/day prednisone of equivalent), HCQ, SSZ, gold or AZA also permitted.	PBO-controlled phase to day 197	DAS28-ESR ABT vs. PBO at 6 months (not powered with superiority or non-inferiority design to compare two active arms)	No	Multinational, multicentre (86 sites)	Bristol-Myers Squibb, USA	Schiff *et al.*, 2008 (RM24766) (full publication) [66]
ATTEST[66]		IFX 3 mg/kg i.v. administered on days 1 (i.e. week 0), 15 (i.e. week 2), 43 (i.e. week 6) and 85 (i.e. week 12) and every 56 days (i.e. 8 weeks) thereafter (NB: licensed dose 3 mg/kg i.v. at weeks 0, 2, 6 and every weeks thereafter, adjustments in dosage and frequency of administration permitted after week 12 in license) (165 randomised) + MTX								
ATTEST[66]		ABT dosed according to weight: patients weighing less than 60 kg, 60-100kg, or more than 100kg received 500 mg, 750 mg or 1000 mg of ABT respectively. ABT administered i.v. on days 1, 15 and 29 and every 28 days thereafter, up to and								

		including day 337 (156 randomised) + MTX								
AMPLE	RCT (non-inferiority)	ABTs.c. + MTX (N=318)	15-25mg/week (or ≥7.5mg/week in patients intolerant to higher doses) 17.5 (6.35) mg/week at baseline	Predisone (mean dose 6.6 mg/day); Corticosteroids (50.9%); SFZ (3.1%); HCQ (13.2%)	2 years (first 12 months' data just published)	ACR20 response at 1 year	No	N & S America	Bristol-Myers Squibb	Weinblatt 2013 full paper[142] Weinblatt 2012 abstract (RM24651)
AMPLE		ADA + MTX (N=328)	15-25mg/week (or ≥7.5mg/week in patients intolerant to higher doses) 17.3 (6.16) mg/week at baseline	Predisone (mean dose 6.4 mg/day); Corticosteroids (50.3%); SFZ (3.4%); HCQ (10.7%)						
REDSEA EU Clinical Trials Register 2006-006275-21/GB A randomised efficacy and discontinuation study of etanercept versus adalimumab	Pragmatic, randomised, parallel group, multicentre, unblinded and non-inferiority trial	ADA+cDMARDs n=60	66.7% patients on MTX, Median dose (mg/week) 20	There were no constraints on changes in the dose of methotrexate, use of other DMARDs including previously untried agents, or on use of oral, parenteral or intra-articular corticosteroids once patients were included in the study. Other DMARDs Azathioprine 1 (1.7%) Hydroxychloroquine 12 (20%) Leflunomide 5 (8.3%) Penicillamine 1 (1.7%) Sulfasalazine 13 (21.7%)	52 weeks	proportion of patients continuing treatment after 52 weeks	Yes	UK	sponsorship of University Hospital Birmingham NHS Foundation Trust part supported by a grant from the Queen Elizabeth Hospital Birmingham Charity	Jobanputra 2012[104] (full article in peer-reviewed journal)
REDSEA		ETN50+cDMARDs n=60	66.7% patients on MTX, Median dose (mg/week) 17.5	Other DMARDs Azathioprine 1 (1.7%) Hydroxychloroquine 1 (1.7%)						

				Leflunomide 8 (13.3%) Penicillamine 0 Sulfasalazine 8 (13.3%)						
ADACTA[55] (NCT01119859)	RCT (Phase IV, double-blind)	TCZ 8 mg/kg i.v. every 4 weeks + s.c. PBO ADA (163 randomised)	NA	All DMARDs washed out before baseline (all ≥ 2 weeks, LEF ≥ 12 weeks or after standard washout)	24 weeks	Mean change from baseline in DAS28 at 24 weeks	Yes	Multicentre, multinational	Roche	Gabay *et al.*, 2013 (full publication) [55]
ADACTA[55]		ADA +. PBO (163 randomised)	NA							
De Filippis 2006	RCT	ETN + MTX (N=16)	Between 10 and 12.5mg/week	Prednisone (max dosage 10mg/day)	54 weeks	ACR20, 50 & 70 & HAQ improvement	No	Sicily	NR	De Filippis [75] 2011 full paper
De Filippis 2006		IFX + MTX (N=16)	Between 10 and 12.5mg/week							

Table 347: Trial characteristics: Population 2/3 biologics vs. DMARD(s) or PBO

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
AIM AIM (Abatacept in Inadequate responders to Methotrexate) NCT00048568 Russell 2007	randomized, double-blind, placebo-controlled trial confirmatory phase III	MTX+PBO n=219	15.7 (3.5) mg/week	Patients were permitted to continue taking oral corticosteroids, provided that the prescribed dose was reduced to the equivalent of (10 mg prednisone daily for 28 days	12months	health related quality of life (HRQoL)	nr	USA and Europe (incl UK)	Bristol-Myers Squibb	Russell 2007 [58] Kremer 2006 [59]
AIM		ABTi.v.+ MTX n=433	16.1 (3.6)							
ASSET	RCT (Phase IIIb)	PBO + MTX (23 randomised)	10-25 mg/week, mean dose at baseline: 17.3 (4.2)	MTX (100%), oral and/or injectable corticosteroids (60.9%), low dose oral corticosteroids (52.2%), NSAIDs (87.0%)	4 months	Reduction in wrist synovitis score from mean MRI scores at baseline and month 4.	No	Europe	Bristol-Myers Squibb	Conaghan 2012 full paper[64]
ASSET		ABT i.v. (~10mg/kg) + MTX (27 randomised)	10-25 mg/week, mean dose at baseline: 16.9 (4.6)	MTX (100%), oral and/or injectable corticosteroids (70.4%), low dose oral corticosteroids (59.3%), NSAIDs (81.5%)						
ASSURE	RCT	PBO + cDMARDs (482 treated)	NR	MTX, HCQ, chloroquine, SSZ, LEF, gold, AZA, (ETN, IFX, ADA)	1 year	Safety	No	NR	Bristol-Myers Squibb	Weinblatt 2006 full paper[65]
ASSURE		ABT + cDMARDs (959 treated)	NR	MTX, HCQ, chloroquine, SSZ, LEF, gold, AZA, (ETN, IFX, ADA)						
AUGUST II	Phase II,	MTX+PBO	NR	allowed steroids unless	25weeks	proportion	nr	Europe and	Merck	van

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
van Vollenhoven 2011 NCT00595413. Atacicept for Reduction of Signs and Symptoms in the Rheumatoid Arthritis Trial II	Randomized, Placebo-Controlled Trial	n=76		prednisone dosage >10 mg/day (or equivalent) or change in steroid or nonsteroidal antiinflammatory drug dosing regimen <=28 days before study day 1		of patients with 20% improvement in disease severity according to the ACR criteria, as assessed using the CRP level (ACR20-CRP)		USA	Serono, Geneva, Switzerland and EMD Serono, Rockland, Massachusetts, which are affiliates of Merck KGaA, Darmstadt, Germany.	Vollenhoven 2011 [68] (full article in peer-reviewed journal)
AUGUST II		ADA+MTX n=79	NR							
CHANGE Miyasaka 2008 Clinical investigation in Highly disease-affected rheumatoid Arthritis patients in Japan with Adalimumab applying staNdard and	Phase II/III, multicenter, double-blind, placebo-controlled	PBO n=87	NA	steroids allowed	24weeks	ACR20 response rate at Week 24	Patients who experienced an increase in disease activity or who had less than 10% reduction in tender joint counts (TJC) and swollen joint counts (SJC) compared with baseline after at least eight weeks of treatment	Japan	Abbott Japan Co., Ltd., Osaka, Japan, and Eisai Co., Ltd., Tokyo, Japan.	Miyasaka 2008 [72](full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
General Evaluation							stopped study therapy with adalimumab/placebo and were switched to an open-label rescue treatment that could include higher doses of steroids, nonsteroidal antiinflammatory drugs, or conventional DMARDs.			
CHANGE		ADAmon n=91	NA							
DE019 Keystone 2004 NCT00195702	phase III multicenter double-blind, placebo-controlled study	MTX+PBO n=200	16.7 (4.1)	Doses and routes of administration of concomitant RA therapies, such as MTX, corticosteroids, and nonsteroidal antiinflammatory drugs (NSAIDs), were kept constant throughout the study. Oral corticosteroids, if used previously, were allowed at a maximum prednisone-dose equivalent of 10 mg/day	52 weeks	radiographic progression at week 52 (total Sharp score by a modified method [TSS]), clinical response at week 24 (improvements of at least 20% in the American	At week 16 or thereafter, patients who were not achieving an ACR20 response (improvements of at least 20% in the ACR core criteria) were allowed to receive "rescue" treatment with a traditional DMARD at the discretion of their treating physician.	USA and Canada	Abbott Laboratories, Abbott Park, Illinois	Keystone 2004 [74] (full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
						College of Rheumatology core criteria [ACR20]), and physical function at week 52 (disability index of the Health Assessment Questionnaire [HAQ]				
DE019		ADA+MTX n=207	16.7 (SD 4.5) weekly dose mg/kg							
STAR Safety Trial of Adalimumab in Rheumatoid Arthritis Furst 2003 24653	randomized, double-blind, placebo-controlled	PBO+cDMARDs n=318	Number of traditional DMARD 0 48 (15.1) 1 172 (54.1) 2 84 (26.4) 3+ 14 (4.4) Mean number of DMARD 1.2	Patients continued to receive their baseline doses of standard antirheumatic therapy, which could include traditional DMARD, low dose corticosteroids (prednisone equivalent dose ≤ 10 mg/day), NSAID, and/or analgesics. Treatment with traditional DMARD permitted during the study included chloroquine, hydroxychloroquine,	24 weeks	frequencies of adverse events, serious adverse events, severe or life-threatening adverse events, adverse events leading to withdrawal, infection, or serious infection	nr	USA	Abbott Laboratories, Abbott Park, Illinois, USA	Furst 2003 [107] (full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
				leflunomide, methotrexate (MTX), parenteral gold, oral gold, sulfasalazine, or any combination of these. Doses of traditional DMARD, corticosteroids, NSAID, and/or analgesics must have been stable for at least 28 days before screening,						
STAR		ADA+cDMARDs n=318	Number of traditional DMARD 0 57 (17.9) 1 184 (57.9) 2 66 (20.8) □3+ 11 (3.5) Mean number of DMARD 1.1							
van de Putte 2004	RCT (Phase III, double-blind)	PBO s.c. (110 randomised)	NR	Use of NSAIDs and oral corticosteroids before study permitted at stable doses (up to 10 mg/day prednisolone or equivalent. Analgesics permitted (not within 12 hours of study visits)	26 weeks	ACR20 response at week 26	Yes (ADA or PBO patients with increased inflammatory synovitis or <10% improvement in TJC and SJC after >8 weeks treatment could enter rescue arm,	Multicentre, multinational (Europe, Canada, Australia)	Abbott	van de Putte *et al.*, 2004 (full publication) [112]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
							during which study drug could be discontinued and doses of NSAIDs/corticosteroids increased/other DMARDs initiated at physician's discretion)			
van de Putte 2004		ADA mon (113 randomised)	NR							
ARMADA Weinblatt 2003 Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab [D2E7] in Rheumatoid Arthritis	randomized, double-blind, placebo-controlled trial phase II/III	MTX+PBO (n=62)	16.5 (SD 5.0) mg/week	salicylates, nonsteroidal antiinflammatory drugs, and corticosteroids (maximum daily dose of 10 mg of oral prednisone or equivalent). Folic acid or leucovorin was permitted.	24week	American College of Rheumatology criteria for 20% improvement (ACR20) at 24 weeks	Patients who failed to meet or to maintain an ACR20 response but had received study drug (adalimumab or placebo) for at least 16 weeks were eligible to remain in the study or to roll over to an open-label continuation study with adalimumab	USA and Canada	Abbott Laboratories and Knoll Pharmaceuticals	Weinblatt 2003 [62] (full article in peer-reviewed journal)
ARMADA		ADA+MTX (n=67)	16.4 (SD 4.mg/week							
Kim 2007	phase III randomized, double-blind,	MTX+PBOrescueWeek18 n=65	16.3 (3.4)	Nr	24weeks	20% improvement in the	Beginning at week 18, patients with documented	Korea	Abbott Laboratories,	Kim 2007 [89] (full article in peer-

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
	placebo-controlled, phase III study					American College of Rheumatology response criteria (ACR20) at week 24	non-response could discontinue their double-blind study medication and switch to rescue therapy with open-label adalimumab 40 mg sc eow.		Abbott Park, Illinois, USA	reviewed journal)
Kim 2007		ADA+MTX n=63	16.6 (3.3)							
CERTAIN (NCT00674362)	RCT (Phase IIIb)	PBO + cDMARDs (98 randomised)	NA	Existing cDMARDs	52 weeks	% patients in CDAI remission (≤2.8)	Patients in CDAI remission at weeks 20 and 24 stopped CTZ and were monitored to week 52	NR	UCB	Smolen 2011 abstract[71] Emery 2012 abstract[355]
CERTAIN		CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + DMARDs (96 randomised)	NA	Existing cDMARDs						
REALISTIC	RCT (Phase 3)	PBO + existing cDMARDs	NA	MTX, LEF, SSZ, chlorquine, HCQ, AZA, gold, steroids , NSAIDs	12 weeks	ACR20 at 12 weeks	NA (12 week study)	USA, Canada and Europe	UCB	Weinblatt 2012 abstract (RM38389)
REALISTIC		CTZ 400mg weeks 0, 2, 4 then 200mg every 2 weeks + existing cDMARDs		MTX, LEF, SSZ, chlorquine, HCQ, AZA, gold, steroids , NSAIDs						
ADORE van Riel 2006 7418 Add Enbrel or Replace	prospective, 16 week, randomised, open-label, parallel group, outpatient study	ETNmon n=160 (n=159 received treatment and provided	NA	NSAIDs and corticosteroids allowed	16 weeks	The primary efficacy measure was the proportion of evaluable	Nr	60 centres in eight countries (Denmark, Finland, France,	Wyeth Research	van Riel 2006 [56] (full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
Methotrexate		data)				patients in each treatment group who achieved an improvement of >1.2 units in DAS28 score from baseline to week 16		Germany, The Netherlands, Turkey, UK and Spain)		[57] vanRiel 2008 (full article in peer-reviewed journal)
ADORE		ETN+MTX n=155	MTX (>=12.5 mg/week orally or by injection) median 15mg/week							
CREATE - IIb D1520C00001 NCT00520572 (Phase IIa and IIb trials)	phase IIb study was a randomised, double-blind, placebocontrolled, parallel-group multicentre trial (with an open-label etanercept treatment group) to evaluate the efficacy of four doses of AZD9056 administered for 6 months on background	DMARD+PBO n=65	Patients were required to have received methotrexate for ≥6 months (the dose must have been stable between 5 and 25 mg/week for ≥6 weeks) or sulphasalazine for ≥16 weeks (at a stable dose of 0.5–3 g/day for ≥6 weeks) prior to randomisation.	Concurrent treatment with stable doses of non-steroidal anti-inflammatory drugs and/or prednisone (maximum 10 mg daily) was allowed throughout the study.	6 months	the proportion of patients meeting ACR 20% response criteria (ACR20) at 6 months (based on 28 joint counts).	Nr	Canada and UK	AstraZeneca	Keystone 2012 [86] (full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
	methotrexate or sulphasalazine									
CREATE - IIb		ETN50+DMARD n=64 note either MTX %s across both arms (89.8%) or SSZ (9.7%) used as DMARD (not both)								
ETN309 (Combe 2006) Etanercept Study 309	randomized, double-blind, controlled trial	SSZ+PBO n=50	Sulfasalazine dose (g/day), mean (SD) 2.1 (0.4)	Patients were permitted stable doses of oral corticosteroids ((10 mg/day of prednisone or equivalent), one non-steroidal anti-inflammatory drug, simple analgesics with no anti-inflammatory action or daily doses of aspirin ((300 mg) during the study.	2 years	percentage of patients achieving >20% improvement as assessed by the ACR 20 response at week 24.	nr	Europe (incl UK), Australia, USA	Wyeth Research, Collegeville, Pennsylvania, USA	Combe 2006 [78](full article in peer-reviewed journal) [79] Combe 2009) (full article in peer-reviewed journal)
ETN309		ETN+PBO n=103	NA							
ETN309		ETN+SSZ n=101	Sulfasalazine dose (g/day), mean (SD) 2.1 (0.5)							
JESMR	RCT (Phase 4)	ETN mon (74 randomised)	7.0 (1.4)	Folic acid (37.7%), corticosteroids (46.4%)	52 weeks	Good EULAR response and ACR50 response at week 24	No	Japan	Japanese Ministry of Health, Labour and Welfare	Kameda 2010 full paper[356] Kameda 2011 full paper[357]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
JESMR		ETN + MTX 6-8mg/week (77 randomised)	7.4 (1.1)	Folic acid (52.1%), corticosteroids (60.3%)						
Lan 2004	RCT, double-blind	PBO+MTX n=29	12.5-20 mg/week	NSAIDs, aspirin and corticosteroids were allowed	12 weeks	reduction of tender and swollen joint counts by 20% (ACR20), 50%, 70% at 12weeks	NR	Taiwan	Wyeth-Ayerst (Asia) Ltd, Taiwan branch	Lan 2004 [91] (full article in peer-reviewed journal)
Lan 2004		ETN+MTX n=29								
LARA Machado 2012 NCT00848354 Latin American RA study	randomised, open-label, active-comparator study phase 4	MTX+DMARD n=142	14.4 (3.9)	NR	24 weeks	proportion of subjects achieving American College of Rheumatology (ACR50) criteria at week 24	NR	Latin American region (Argentina, Chile, Colombia, mexico, panama)	Wyeth	Machado 2012 (conference abstract)[92]
LARA		ETN50+MTX n=281	14.1 (3.8)							
Moreland 1999 Mathias 2000	confirmatory phase III randomized, double-blind, placebo-controlled	PBO n=80	NA	corticosteroids and NSAIDs allowed	6 months	20% and 50% improvement ACR, at 3 months and 6 months	Nr	USA	Immunex Corp, Seattle, Washington	Moreland 1999 [94] (full article in peer-reviewed journal) Mathias 2000 [95](full article in peer-reviewed

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
										journal)
Moreland 1999 Mathias 2000		ETN+PBO n=78	NA							
RACAT O'Dell et al 2013 Rheumatoid Arthritis: Comparison of Active Therapies in Patients With Active Disease Despite Methotrexate Therapy NCT00405275	randomised, double-blind, placebo-controlled, non-inferiority trial	MTX+SSZ+HCQ n=178 potential to switch groups at week 24	19.5 (5.0)	Participants continued to receive nonsteroidal antiinflammatory agents and prednisone (≤10 mg per day) at stable doses	48 weeks	The originally proposed primary outcome was the difference in the proportion of participants who had a DAS28 of 3.2 or less at week 48. In response to unexpectedly low enrollment, the protocol was amended in October 2008 to change the primary outcome from a binary	Part of study design - If the score on the DAS28 decreased (indicating improvement) by 1.2 or more by 24 weeks, the initial therapy was continued. If the score on the DAS28 decreased by less than 1.2, the participant was switched to the alternative regimen.	USA and Canada	Supported by the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, and the Canadian Institutes for Health Research and by an interagency agreement with the National Institutes of Health–American	O'Dell 2013 (full article in peer-reviewed journal) [101] O'Dell 2012 [102](conference abstract)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
						outcome to a continuous outcome in order to increase the power of the study			Recovery and Reinvestment Act.	
RACAT		ETN50+MTX n=175 potential to switch groups at week 24	19.7 (4.5)							
Wajdula 2000 European Etanercept Investigators Group) Protocol 0881A1-300-EU 358	RCT, multi-centre, double blind	PBO n=105			12 weeks	change from baseline in the number of swollen and painful joints at 3 months	NA (12week study)	Europe, multicentre		Info taken from published HTA report that had access to manufacturer trial reports Chen 2006
Wajdula 2000		ETN n=111								
Weinblatt 1999	RCT, double-blind	MTX +PBO , n=30	Stable dose 12.5-25mg/week	NSAIDs and corticosteroids allowed	24 weeks	American College of Rheumatology criteria for a 20 percent	[condition not described; Patients who received intraarticular injections of	Multicentre USA	Supported by Immunex	Weinblatt 1999, [114] (full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
						improvement in measures of disease activity (ACR 20) at 24 weeks	corticosteroids during the study were counted as having or not having a response according to their overall evaluation,]			Kremer 2003 [115] (full article in peer-reviewed journal)
Weinblatt 1999		ETN+MTX, n=59								
APPEAL NCT00422227 Kim 2012 RefID24708	open-label, active-comparator, parallel-design, multi-centre RCT	MTX plus DMARD (SSZ, HCQ or leflunomide), n=103	6.9 (8.5)	NSAIDs or corticosteroids were allowed, but not multiple non-steroidal anti-inflammatory drugs (NSAIDs), and any increase in dosage of baseline NSAID or corticosteroid	16 weeks	ACR response (ACR-N) area under the curve (AUC) over 16 weeks	NR	Asia-Pacific region	Wyeth	Kim 2012 [61] full article in peer-reviewed journal) Bae 2013 [141] (full article in peer-reviewed journal)
APPEAL		ETN+MTX , n=197	6.5 (7.3)							
GO-FORTH	RCT (Phase 2/3)	PBO Q4W + MTX 6-8mg/week (90 randomised)	NR	Concurrent NSAIDs, analgesic and oral corticosteroids (≤10 mg prednisolone/day or equivalent) allowed with stable doses ≥2 weeks prior to and during the study	24 weeks	ACR20 response at week 14	Patients with <20% improvement from baseline in TJC and SJC at week 14 could enter double-blind early escape where the dose was increased (or added in PBO arm).	Japan	Centocor Research & Development Inc., Janssen Pharmaceuticals KK and Mitsubishi Tanabe	GO-FORTH[81] Tanaka 2012 full paper

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
									Pharmaceutical Corporation	
GO-FORTH		GOL 50mg s.c. Q4W + MTX 6-8mg/week (89 randomised)	NR							
GO-FORWARD (NCT00264550)	RCT (Phase III, double-blind)	Placebo s.c. every 4 weeks + MTX (133 randomised)	Mean (SD)= 17.0 (2.75) 15.0 (15.0 to 20.0) (median, IQR)	Patients receiving NSAIDs or other analgesics for RA required to have been taking stable dose for at least 2 weeks before first dose of study agent. Patents receiving oral corticosteroids required to have been taking stable dose equivalent to 10 mg/day or less of prenisone for at least 2 weeks before first dose of study drug.	Double-blind placebo-controlled phase to week 24 and open-label extension up to 5 years	2 co-primary endpoints: proportion of patients achieving ACR20 response at week 14 and improvement from baseline in HAQ-DI score at week 24.	Yes	Multinational, multicentre (60 sites over 12 countries)	Centocor	Keystone *et al.*, 2009 (RM476)[191] (full publication, results to week 24) Keystone *et al.*, 2010 (RM24700) [82] (full publication, results to week 52)
GO-FORWARD		GOL 50 mg s.c. every 4 weeks + MTX (89 randomised)	Mean (SD)= 17.4 (3.00) 15.0 (15.0 to 20.0) (median, IQR)							
Kay 2008 (NCT00207714)	RCT (Phase II, double-blind)	PBO s.c. + MTX (35 randomised)	All patients continued to receive stable doses of MTX (at least 10 mg/week)	Oral corticosteroids permitted at stable pre-study dosage not exceeding equivalent 10 mg prednisone per day.	52 weeks	Proportion of patients meeting ACR 20% improveme	Yes	Multicentre (40 study sites, geographical location(s)	Centocor	Kay *et al.*, 2008 (RM2469(full publication)

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
			through end of study.	Commercially available NSAIDs permitted at stable pre-study dose. Folic acid at stable dosage of at least 5 mg every week for at least 4 weeks before first study drug dose.		nt criteria (achieving an ACR20 response) at week 16.		not stated)		[88]
Kay 2008		GOL 50 mg s.c. every 4 weeks + MTX (35 randomised)								
Abe 2006	RCT (Phase NR, double-blind)	PBO + MTX (N randomised NR, 47 patients received ≥ 1 infusion)	7.4 (SD = 2.2)	Patients taking NSAIDs, folic acid or corticosteroids (10 mg/day or less prednisolone equivalent) required to have received stable dose for at least 4 weeks before study entry.	14 weeks	ACR20 response at week 14	No	Multicentre, Japan	NR	Abe *et al.*, 2006 (full publication) (RM24854)[53]
Abe 2006		IFX 3 mg/kg i.v. at weeks 0, 2 and 6 + MTX (N randomised NR, 49 patients received ≥ 1 infusion)	7.1 (SD = 1.9)							
ATTRACT	RCT (Phase III, double blind)	PBO i.v. + MTX (88 randomised)	Median 15 (IQR 12.5-17.5)	Patients receiving oral corticosteroids (10 mg/kg or less prednisone equivalent) or NSAIDS required to have stable dose for at least 4 weeks before screening (and must not have received either drug for at least 4 weeks before screening). Patients received	54 week PBO-controlled RCT with LTE to 102 weeks	ACR20 response at week 30 without requiring a surgical joint procedure, initiation of new antirheumat	No	Multicentre, multinational,	Centocor	Maini *et al.*, 1999 (full publication) (RM2473[67]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
				baseline dose of MTX or corticosteroids during study.		ic drugs or increased in antirheumatic drugs. ACR20 response at week 30				
ATTRACT		IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter (86 randomised) +MTX	Median 15 (IQR 12.5-17.5)							
Durez 2004	RCT (Phase NR, open label)	Single i.v. infusion of 1 g methylprednisolone (MP) (sodium hemisuccinate) at week 0 + MTX (14 randomised)	Median 12.5 (range 10-15)	Oral glucocorticoid doses remained unaltered during study. i.a. steroids not permitted. Introduction of new NSAID or DMARD not permitted.	14 weeks	NR	No	Belgium	Schering-Plough	Durez *et al.*, 2004 (full publication) (RM24630) [76]
Durez 2004		IFX 3 mg/kg at weeks 0, 2 and 6 + MTX (12 randomised	Median 15 (range 10-15)							
START	RCT	PBO + MTX (363 randomised)	Median (IQR): 15.0 (10-15)	MTX only (70.0%), MTX + 1 DMARD (25.3%), MTX + 2 DMARDs (4.4%), NSAIDs (39.4%), corticosteroids (59.2%), narcotics/opioid analgesics (6.1%)	1 year (22 weeks before dose escalation commenced)	Occurrence of a serious infection within 22 weeks of initiating therapy	No, but dose escalation from 22 weeks if <20% improvement in SJC and TJC or ≥50% discontinuation in improvement in combined SJC and TJC	NR	Centocor Research and Development Inc	Westhovens 2006 full paper[108] ~~Yocum abstract Rahman 2007 full paper~~
START		IFX 3mg/kg + MTX (360 randomised)	Median (IQR): 15.0 (10-18)	MTX only (70.8%), MTX + 1 DMARD (24.4%), MTX + 2						

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
				DMARDs (4.7%), NSAIDs (43.3%), corticosteroids (59.2%), narcotics/opioid analgesics (5.8%)						
Swefot (Swedish Pharmacotherapy) study (WHO database number CT20080004)	RCT (phase NR, open label)	Sulfasalazine (1000 mg twice daily orally) + hydroxychloroquine (400 mg daily orally) + MTX (with optional increase to SSZ 1500 mg twice daily if ineffective and cDMARD adjustment in event of toxicity with potential switch to cyclosporin A (5 switched to cyclosporin A, included in primary analyses) n=130	Up to 20 mg/wk	If patients were receiving glucocorticoids, dose was required to be stable for at least 4 weeks at no more than 10 mg daily prednisolone (or equivalent).	2 years	EULAR good response at 12 months	Dose adjustments permitted (see left)	Multicentre (15 rheumatology units), Sweden)	Swedish Rheumatism Association. Schering-Plough	van Vollenhoven *et al.*, 2009) (full publication) (RM24819) [109] 140
Swefot		IFX 3 mg/kg i.v. at weeks 0, 2, 6 and every 8 weeks thereafter with optional increase to IFX every 6 weeks thereafter) (in event of toxicity, optional switch to ETN 50 mg weekly) (5 switched to ETN, included in primary analyses)+MTX n=128								
Wong 2009	RCT (Phase NR, double-blind)	PBO + MTX (with crossover to open-label IFX at week 24). n=9	NR	All antirheumatic medications kept stable for at least 4 weeks before and during study	56 weeks	Vascular ultrasound assessments at weeks 24	Yes (PBO patients could escape to open-label IFX at week	UK	Centocor Pty Ltd Arthritis	Wong *et al.*, 2009 (full publication) (RM44[116]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
				(unless dose alterations were clinically indicated).		and 56	16)		Foundation of Australia.	
Wong 2009		IFX 3 mg/kg at weeks 0, 2, 6 and 8 weeks thereafter + MTX n=17								
Zhang 2006	RCT (Phase NR, double-blind)	PBO i.v. + MTX n=86	Stable dose of MTX continued during study	Glucocorticosteroid dose required to be stable for 4 weeks before screening and dosage not permitted to exceed 10 mg/day prednisone or equivalent.	18 weeks	NR	No	Multicentre (5 centres), China		Zhang *et al.*, 2006 (full publication) (RM2485[117]
Zhang 2006		IFX 3 mg/kg i.v. at weeks 0, 2, 6 and 14 + MTX n=87								
ACT-RAY (NCT00810199)	RCT (Phase III, double-blind)	TCZ 8 mg/kg i.v. every 4 weeks + oral PBO (277 randomised)	Patients received mean weekly doses of MTX/PBO ranging from: TCZ 8 mg/kg i.v. every 4 weeks + oral PBO = 15.8 to 16.3 mg/week TCZ 8 mg/kg i.v. every 4 weeks + MTX = 15.2 to 15.9 mg/week	Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs permitted if doses had been stable for at least 25 of 28 days before start of study agent	2 years	% patients in remission according to DAS28-ESR (DAS28 <2.6) at week 24	No	NR	Roche	Dougados *et al.*, 2013 (RM24867) (full publication) [54]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
ACT-RAY		TCZ 8 mg/kg i.v. every 4 weeks + MTX n=276								
MEASURE	(RCT, phase NR, double-blind)	PBO + MTX (69 randomised)	NR	NR	24 weeks double-blind phase of 2 year study	NR	Yes (27 patients in PBO arm entered early escape treatment with open label TCZ at week 16)	UK, USA, Canada	Lead author: grant/research support from Roche	McInnes *et al.*, 2011 (conference abstract) (RM24929) [93]
MEASURE		TCZ 8 mg/kg i.v. every 4 weeks + MTX (69 randomised)	NR							
Nishimoto 2004	RCT (Phase NR, double-blind)	PBO i.v. every 4 weeks (53 randomised)	NA	Stable prednisolone (≤ 10 mg/day) and NSAIDs permitted at stable doses. No parenteral and/or i.a. corticosteroids permitted during 4 week washout period before initiation of study agent and during study period.	3 months	ACR20 at week 12	No	Multicentre, Japan	Chugai Pharmaceutical, Japan	Nishimoto *et al.*, 2004 (full publication) (RM24919) [96]
Nishimoto 2004		TCZ 8mg/kg i.v. every 4 weeks (55 randomised)	NA							
SAMURAI Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis,	multi-centre, x-ray reader-blinded, randomised, controlled trial phase III	cDMARDsDiseaseActivity n=145	8.0 (2. 123 patients (85%) received MTX: 81 (56%) received a combination of MTX and DMARDs, 42 (29%) received MTX monotherapy, and	For the conventional DMARD group, the dose, type and combination of DMARDs and/or immunosuppressants, except for anti-TNF agents and leflunomide, could be varied according to disease activity at the discretion of the treating	52 weeks	progression of structural joint damage	nr	Japan	Chugai Pharmaceutical Co., Ltd., Tokyo, Japan	Nishimoto 2007 (full article in peer-reviewed journal) [105]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
			20 (14%) received DMARDs and/or immunosuppressants other than MTX, besides corticosteroids	physician						
SAMURAI		TCZi.v. n=157	NA	both groups - Oral corticosteroids ((10 mg prednisolone per day) were allowed, but the dosage could not be increased during the study. Use of one nonsteroidal anti-inflammatory drug (NSAID), including switching to another NSAID, was allowed.						
SATORI (NCT00144521)	RCT (Phase III, double-blind)	PBO + MTX n=64	8 (maximum permitted dose in Japan)	Oral corticosteroids permitted at ≤ 10 mg/day prednisolone (as worded) (dose increase not permmited) i.a. corticosteroid injections (one joint max at one treatment) and hyaluronate preparations permitted. Use of 1 NSAID permitted (switching to another NSAID allowed). DMARDs, i.v. or i.m.	Double-blind controlled phase to week 24	ACR20 response at week 24	No	Single country, multicentre (25 sites across Japan)	Chugai Pharmaceutical Co., Ltd., Japan	Nishimoto *et al.*, 2009 (RM2475(full publication) [106]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
				corticosteroids, plasmapharesis and surgical treatment not allowed.						
SATORI		TCZ 8 mg/kg i.v. every 4 weeks+ PBO capsules n=61								
TOWARD	RCT (Phase III, double-blind)	PBO i.v. every 4 weeks + stable cDMARDs (415 randomised)	14.7	Oral glucocorticoids (≤ 10 mg/day prednisone or equivalent) and NSAIDs/COX-2 inhibitors permitted if doses stable for ≥ 6 weeks.	24 weeks	ACR20 at week 24	Yes (early escape at week 16 for patients failing to achieve >20% improvement in both SJC and TJC consisting of adjustment of background DMARD dosage and/or a different DMARD and/or i.a./oral glucocorticoids)	Multinational (18 countries), multicentre	Roche	Genovese *et al.*, 2008 (full publication) (RM2466[111]
TOWARD		TCZ 8 mg/kg i.v. every 4 weeks + stable DMARDs (805 randomised)	15.0							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name / Author, year (NCT/sponsor number)	Trial design (RCT, phase, LTE)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
				[redacted]						
[redacted] unpublished		[redacted]	[redacted]	[redacted]						

Table 348: Trial characteristics: RCTs (ineligible for systematic review) used as additional evidence in NMA Sensitivity analyses

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
ACQUIRE	ABT s.c. + PBO i.v. + MTX n=736	≥15 mg/week (mean at baseline: 16.3 (3.6) mg/week)	Corticosteroids (oral and/or injectable): 72.1%, mean (SD) dose 4.8 (4.5) mg/day.	6 months	ACR20 (% patients achieving response) at 6 months.	No	NR	Bristol-Myers Squibb	Genovese 2011 [120] full paper
ACQUIRE	ABT i.v. + PBO s.c. + MTX n=721	≥15 mg/week (mean at baseline: 16.5 (3.8) mg/week)	Corticosteroids (oral and/or injectable): 74.6%, mean (SD) dose 5.2 (6.9) mg/day.						
NCT00254293	PBO + MTX (119 randomised)	10-30mg/week, mean (SD) 15.8 (4.1)	Addition of another DMARD (HCQ, SSZ, gold, AZA) and/or adjustment in corticosteroids equivalent to ≤10mg/day prednisone were permitted. Use of the above not reported.	12 months	ACR20 response at 6 months	No	Multicentre	Bristol-Myers Squibb	Kremer 2005 [125] full paper Kremer 2003 full paper (RM24716)
NCT00254293	ABT i.v. (~10mg/kg) + MTX (115 randomised)	10-30mg/week, mean (SD) 15.0 (4.4)							
ORAL STANDARD NCT00853385	MTX+PBO n=108	7.5 to 25 mg of methotrexate weekly all groups	Glucocorticoids and Lipid-lowering medication allowed	12months	20% improvement at month 6 in the American College of Rheumatology scale (ACR 20); the change from baseline to month 3 in the score on the Health Assessment Questionnaire–Disability	Patients in the placebo group who did not have a 20% reduction in the number of swollen and tender joints after 3 months (considered as not having had a response)	Europe, USA, Korea, Latin America	Supported by Pfizer.	van Vollenhoven 2012 [127] (full article in peer-reviewed journal)

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
					Index (HAQ-DI) (which ranges from 0 to 3, with higher scores indicating greater disability); and the percentage of patients at month 6 who had a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate	were randomly assigned to either 5 mg or 10 mg of tofacitinib.			
ORAL STANDARD	TOF5+MTX n=204								
ORAL STANDARD	TOF10+MTX n=201								
ORAL STANDARD	ADA+MTX n=204								
Yamamoto 2011 / JRAPID (NCT00791999)	PBO + MTX every 2 weeks (77 patients randomised)	NR	MTX	24 weeks	ACR20 response at week 12	Early escape at week 16 for patients who failed to achieve ACR20 response at both weeks 12 and 14	Japan, multicentre	NR	Yamamoto *et al.*, 2011 (conference abstract, RM17705)[123]
JRAPID	CTZ 200 mg + MTX every 2	NR	MTX						

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
	weeks (82 patients randomised)								
RA0025	PBO + MTX (40 randomised?)	10-20 mg/week	MTX	24 weeks	ACR20 response at week 24	Patients with no ACR20 response at both weeks 12 and 14 were withdrawn	Korea	Not reported	Kang 2012 abstract[128]
RA0025	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + MTX (81 randomised?)	10-20 mg/week	MTX						
RAPID1	PBO + MTX (199 randomised)	13.4	MTX, oral corticosteroids (≤10 mg/day prednisone or equivalent with stable dose from 4 weeks prior to baseline), NSAIDs/cyclooxygenase 2 inhibitors and analgesics.	52 week	ACR20 response rate at week 24 and mean change form baseline in mTSS at week 52	Early escape at week 16 for patients who failed to achieve ACR20 response at both weeks 12 and 14	NR	UCB	Keystone 2008 full paper[129]
RAPID1	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + MTX (393 randomised)	13.6							
RAPID2	PBO + MTX (127 randomised)	12.2	MTX	24 week	ACR20 response at week 24	Early escape at week 16 for patients who failed to achieve ACR20 response at both weeks 12 and 14	International	UCB	Smolen 2009 full paper[130]
RAPID2	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W	12.5	MTX						

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
	+ MTX (246 randomised)								
TEAR (SA mixed pop) NCT00259610 The Treatment of Early Aggressive Rheumatoid Arthritis Trial	MTXmon(ST) n=124 ST =step-up from MTX to triple disease-modifying antirheumatic drug therapy (MTX plus SSZ plus HCQ);	MTX, which was escalated to a dosage of 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12.	for those receiving corticosteroids, the dosage up to 10 mg/day of prednisone) had to be stable for at least 2 weeks prior to screening; for those receiving nonsteroidal anti-inflammatory drugs, the dosage had to be stable for at least 1 week prior to screening folic acid at a dosage of 1 mg per day	102 weeks	an observed-group analysis of DAS28-ESR values from week 48 to week 102	step-up therapy part of study design	USA	Supported by Amgen through a grant to the University of Alabama at Birmingham. The study drugs were provided by Amgen (etanercept and placebo), Barr Pharmaceuticals (methotrexate), and Pharmacia (sulfasalazine and placebo). The initial phases of the study were supported by the NIH (planning grant 1-R34-AR-055122 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to.	Moreland 2012 [131] (full article in peer-reviewed journal)
TEAR (SA mixed pop)	MTXmon(SE) n=255 SE=step-up from MTX to MTX plus etanercept;								
TEAR (SA mixed pop)	MTX+SSZ+HCQ n=132								

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
TEAR (SA mixed pop)	ETN50+MTX n=244								
TEMPO Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes	MTXmon n=228	Methotrexate dose (median [IQR], mg/week) 10 (7·5–15·0) 1	NSAIDs and corticosteroids allowed 5-mg folic acid supplement twice a week	52weeks	numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks,	NR	Europe, Australia, USA	Wyeth Research	Klarekskog 2004 [132] (full article in peer-reviewed journal)
TEMPO	ETNmon n=223	Methotrexate dose (median [IQR], mg/week) 10 (7·5–13·8) 10							
TEMPO	ETN+MTX n=231	Methotrexate dose (median [IQR], mg/week) 10 (7·5–15·0)							
AMBITION (NCT00109408)	MTX alone (284 randomised)	7.5-20	Oral glucocorticoids (≤ 10 mg/day prednisone or equivalent) and NSAIDs permitted if dose stable for ≥ 6 weeks.	24 weeks	ACR20 at week 24	No	Multicentre, multinational	Roche	Jones *et al.*, 2010 (full publication (RM24683 [121])
AMBITION	TCZ 8mg/kg i.v. every 4 weeks (288 randomised)	NA							
LITHE (NCT00106535)	PBO i.v. every 4 weeks + MTX (393 randomised)	Patients received stable dose of MTX 10-25 mg/wk Mean (SD) = 15.0 (4.2)	Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs permitted if doses had been stable for ≥ 6 weeks before study entry.	52 weeks	Co-primary endpoints at week 52: Change from baseline in total Genant-modified Sharp score and AUC	Yes (Rescue therapy at week 16 for patients not achieving ≥ 20%	Multicentre, multinational (14 countries)	Roche	Kremer *et al.*, 2011 (full publication) (RM24722 [124])

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
					for change from baseline in HAQ-DI.	improvement in TJC and SJC. PBO group received TCZ 4 mg/kg + steroids. TCZ 8 mg/kg group received TCZ 8 mg/kg + steroids. If <20% improvement persisted after 3 doses of blinded first-step rescue therapy, patients received second-step rescue of TCZ 8 mg/kg. If still no response, treatment discontinued).			
LITHE	TCZ 8 mg/kg i.v. every 4 weeks + MTX (398 randomised)	Mean (SD) = 15.4 (10.6)							
OPTION	PBO i.v. every 4 weeks + MTX (204 randomised)	14.8 (4.2)	Oral glucocorticoids (≤ 10 mg/day prednisone or equivalent) and NSAIDs permitted if doses stable for ≥ 6 weeks before study entry.	24 weeks	ACR20 at week 24	Yes (Patients not achieving ≥ 20% improvement in both SJC and TJC by	Multicentre (73 centres), multinational (17 countries)	Roche, Chugai Pharmaceutical	Smolen *et al.*, 2008 (full publication (RM24918 [126])

Trial name / Author, year (NCT/sponsor number)	Treatment arms for which data extraction performed (number of patients randomised per treatment arm)	MTX dose during study (where applicable) (mg/week)	Concomitant treatments	Duration of RCT phase	Primary outcome	Early withdrawal plan reported?	Geographical location	Funding source	Primary and supplementary publication details (author, year, publication type (eg. full, abstract))
						week 16 eligible for rescue therapy with TCZ 8mg/kg and steroids if necessary or increase in oral corticosteroid dose (max 10 mg/day)			
OPTION	TCZ 8 mg/kg i.v. every 4 weeks + MTX (205 randomised)	14.5 (4.4)							

Table 349: Population characteristics additional information Population 1 Head to head trial

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
Kume 2011 [90]	ADA mon	NR	85.8	No prior treatment with MTX or biologics. Dosage of all DMARDs had to be stable for ≥8 weeks prior to enrolment.	NR	NR
Kume 2011	ETN mon	NR	88.6	No prior treatment with MTX or biologics. Dosage of all DMARDs had to be stable for ≥8 weeks prior to enrolment.	NR	NR

Table 350: Population characteristics additional information Population 1 biologic vs DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
Bejarano 2008[69]	PBO+MTX n=73	NR	95	MTX naive mean 0.2 prior cDMARDs	NR	NR
Bejarano 2008[69]	ADA+MTX n=75	NR	96	MTX naive mean 0.2 prior cDMARDs	NR	NR
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28 n=32	NR	77.4	MTX naive; no prior biologics	NR	31.3
GUEPARD	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28 n=33	NR	70.0	MTX naive; no prior biologics	NR	30.3
HIT HARD[84]	MTX + PBO	NR	69.4	Required to be DMARD naïve, mean number of prior DMARDs was 0.	NR	NR
HIT HARD	ADA + PBO	NR	63.2	Required to be DMARD naïve, mean number of prior DMARDs was 0.	NR	NR
OPERA [97]	MTX + PBO + steroid	NR	74	Active RA by ACR (1987) revised criteria. Excluded if had glucocorticoids within the last 4 weeks or previous DMARD therapy.	NR	NR
OPERA [97]	ADA + MTX + steroid	NR	70	Active RA by ACR (1987) revised criteria. Excluded if had glucocorticoids within the last 4 weeks or previous DMARD therapy.	NR	NR
OPTIMA	MTX + PBO	90% white	89	Patients were excluded if they had received prior MTX, >2 synthetic DMARDs or biologics.	79	46
OPTIMA	ADA + MTX	89% white	87	Patients were excluded if they had received prior MTX, >2 synthetic DMARDs or biologics.	78	41
PREMIER	MTX + PBO	94.4% white	84.0	Required to be MTX naïve (and no previous treatment with cyclophosphamide, cyclosporine, azathioprine or >2 other DMARDs). 31.5% had prior DMARD experience.	NA	35.4
PREMIER	ADA mon + PBO step up week 16	93.5% white	83.5	Required to be MTX naïve (and no previous treatment with cyclophosphamide, cyclosporine, azathioprine or >2 other DMARDs). 33.2% had prior DMARD experience.	NA	36.5
PREMIER	ADA + MTX step up week 16	93.6% white	85.1	Required to be MTX naïve (and no previous treatment with cyclophosphamide, cyclosporine, azathioprine or >2 other DMARDs). 32.5% had prior DMARD experience.	NA	35.8
COMET	MTX +PBO n=268	White 88%	NR	MTX naive % having prior cDMARDs 24%	76	50
COMET	ETN+MTX	White 87%	NR	MTX naive	72	49

	n=274			% having prior cDMARDs 18%		
ERA, Bathon 2000 Multicentre	MTX + PBO	88% Caucasian	89	Required to be MTX naïve. 46% of patients had prior DMARDs, mean no. of DMARDs 0.6 (0.7).	80	41
ERA, Bathon 2000 Multicentre	ETN + PBO	86% Caucasian	87	Required to be MTX naïve. 40% of patients had prior DMARDs, mean no. of DMARDs 0.5 (0.7).	86	39
GO-BEFORE	PBO+MTX	White =71.3%, Black =3.8%, Asian =15.6% Other (no further details) =9.4%	NR	MTX-naïve patients. Patients had not received more than 3 weekly doses of oral MTX as RA treatment. Patients who had previously received infliximab, etanercept, adalimumab, rituximab, natalizumab or cytotoxic agents excluded. Patients receiving anakinra could participate 4 weeks after receiving last dose. Patients receiving alefacept or efalizumab could participate 3 months after last dose. Previous DMARDs =83/160 (51.9%) Hydroxychloroquine =26/160 (16.3%) Sulfasalazine =51/160 (31.9) Leflunomide = 12/160 (7.5%) Other DMARDs (no further details) =26 (16.3) Anakinra =0/0 (0.0%) Immunosuppresive agents = 3/160 (1.9%)	95.6	68.1
GO-BEFORE	GOL + MTX	White = 74.8% Black = 0.6% Asian = 18.9% Other (no further details) = 5.7%	NR	Previous DMARDs = 80/159 (50.3%) Hydroxychloroquine =33/159 (20.8%) Sulfasalazine = 36/159 (22.6%) Leflunomide = 13/159 (8.2%) Other DMARDs (no further details) =29/159 (18.2%) Anakinra = 0 (0.0) Immunosuppressive agents =2/159 (1.3%)	98.1	69.8
ASPIRE	PBO + MTX	NR	71	Patients had persistent synovitis ≥ 3 months and ≤ 3 years, ≥ 10 swollen joints, and ≥ 12 tender joints. All patients were MTX-naïve. 65-71% DMARD-naïve. Patients were excluded if any prior treatment with MTX (had to be 3 or fewer pre-study doses), had received other DMARDs within 4 weeks of entry (or leflunomide within past 6 months), or had been treated with infliximab, etanercept, adalimumab or other anti-TNF agent. 65% DMARD naïve	82	38
ASPIRE	IFX i.v. 3 mg/kg at weeks 0, 2 and 6 and every 8 weeks	NR	71	71% DMARD naïve	85	37

	thereafter + MTX					
BeST	Sequential monotherapy (DAS-steered)	NR	67	Patients had active disease with ≥ 6 of 66 swollen joints, ≥ 6 of 68 tender joints and ESR ≥ 28 mm/hr or global health score of ≥ 20 mm (0-100 VAS). Exclusion criteria included previous treatment with DMARDs other than antimalarials. (Hydroxychloroquine and chloroquine = antimalarials) Previous antimalarial therapy = 7%	NR	NR
BeST	Step-up combination therapy (DAS-steered)	NR	64	Previous antimalarial therapy = 11%	NR	NR
BeST	Initial combination therapy with prednisone (DAS-steered)	NR	65	Previous antimalarial therapy = 8%	NR	NR
BeST	Initial combination therapy with IFX (DAS-steered)	NR	64	Previous antimalarial therapy = 9%	NR	NR
Durez 2007	MTX	NR	64	MTX-naïve population. Patients had not been previously treated with MTX. Exclusion criteria included previous treatment with > 2 DMARDs (no further details), MTX or i.v. MP.	NR	NR
Durez 2007	MTX + i.v. methyprednisolone (MP)	NR	100		NR	NR
Durez 2007	IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22, 30, 38, 46+MTX	NR	67		NR	NR
IDEA	MP 250 mg i.v. at week 0, PBO i.v. at weeks 2, 6, 14, 22 + MTX	NR	NR	Patients described as DMARD-naïve (no further details)	NR	NR
IDEA	IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22 + MTX (IFX dose modifications permitted according to DAS44 from week 26)	NR	NR		NR	NR
Quinn 2005	MTX + PBO	NR	60	No prior treatment with DMARDs or oral corticosteroids.	NR	NR
Quinn 2005	IFX + MTX	NR	70	No prior treatment with DMARDs or oral corticosteroids.	NR	NR

Table 351: Population characteristics additional information Population 2 Head to head trials

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
ATTEST[66]	PBO+MTX	76.4% Caucasian	77.3	MTX ≥ 15 mg/week for ≥ 3 months (stable for ≥ 28 days) and washed out all DMARDs (at least 28 days prior) except for MTX. No prior ABT or anti-TNF therapy permitted. MTX, n (%) = 110/110 (100) Dose, mg/wk (SD) = 16.6 (3.7) Duration, months (SD) = 23.7 (25.6)	84.5	70.0
ATTEST[66] (NCT00095147)	IFX 3 mg/kg i.v. administered on days 1 (i.e. week 0), 15 (i.e. week 2), 43 (i.e. week 6) and 85 (i.e. week 12) and every 56 days (i.e. 8 weeks) thereafter (NB: licensed dose 3 mg/kg i.v. at weeks 0, 2, 6 and every weeks thereafter, adjustments in dosage and frequency of administration permitted after week 12 in license) + MTX	80.6% Caucasian	84.8	MTX, n (%) = 164/165 (99.4) Dose, mg/wk (SD) = 16.3 (3.6) Duration, months (SD) = 23.6 (26.8)	86.1	71.5
ATTEST[66] (NCT00095147)	ABT dosed according to weight: patients weighing less than 60 kg, 60-100kg, or more than 100kg received 500 mg, 750 mg or 1000 mg of ABT respectively. ABT administered i.v. on days 1, 15 and 29 and every 28 days thereafter, up to and including day 337 (156 randomised) + MTX	80.8% Caucasian	87.2	MTX, n (%) = 156/156 (100) Dose, mg/wk (SD) = 16.5 (3.7) Duration, months (SD) = 18.3 (20.0)	85.3	75.6
AMPLE	ABT s.c.	80.8% Caucasian	75.5	Inadequate response to MTX, no prior bDMARDs. Concomitant medication included sulfasalazine (3.1%) and hydroxychloroquine (13.2%).	NR	50.9
AMPLE	ADA	78.0% Caucasian	77.4	Inadequate response to MTX, no prior bDMARDs. Concomitant medication included sulfasalazine (3.4%) and hydroxychloroquine (10.7%).	NR	50.3
RED-SEA[104]	ADA+cDMARDs n=60	NR	91.7	100% prior MTX	58.3%	On oral prednisolone 33.3%
RED-SEA[104]	ETN50+cDMARDs n=60	NR	85	100% prior MTX	43.3%	On oral prednisolone 45%
ADACTA[55]	TCZ + PBO	NR	75	Patients with RA of at least 6 months duration and DAS28 > 5.1 who were MTX intolerant or for whom continued treatment with MTX was considered	NR	55

				ineffective or inappropriate. Mean number of previous DMARDs = 2.0 (1.1) Stopped taking MTX < 2 months before baseline = 99/163 (61%)		
ADACTA[55]	ADA + PBO	NR	73	Mean number of previous DMARDs = 2.0 (1.1) Stopped taking MTX < 2 months before baseline = 102/162 (63%)	NR	57
DeFilippis 2006	ETN + MTX	NR	NR	Non-responder to DMARDs for >6 months (no further detail reported). All receiving a stable dose of concomitant MTX in 3 months before entering the study.	NR	NR
DeFilippis 2006	IFX + MTX	NR	NR	Non-responder to DMARDs for >6 months (no further detail reported). All receiving a stable dose of concomitant MTX in 3 months before entering the study.		

Table 352: Population characteristics: additional information Population 2 biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
AIM	MTX+PBO n=219	88.1% white	78.5	100% prior MTX 8.7 % prior cDMARDs other than MTX	82.6	68.5
AIM	ABTi.v.+ MTX n=433	87.5% white	81.8	100% prior MTX 12.2 % prior cDMARDs other than MTX	85.5	72.1
ASSET	PBO + MTX	82.6% Caucasian	82.6	Non-response to MTX (≥15 mg/week or a maximum tolerated dose of ≥10 mg/week for ≥3 months prior to day 1)..	87.0	60.9
ASSET	ABT i.v. (~10mg/kg) + MTX	96.3% Caucasian	55.6	Non-response to MTX (≥15 mg/week or a maximum tolerated dose of ≥10 mg/week for ≥3 months prior to day 1)..	81.5	70.4
ASSURE	PBO + cDMARDs	83.3% white	NR	Active disease (functional classes I, II, III, IV ACR) despite ≥1 biologic and/or nonbiologic therapy, stable dose for ≥28 days before trial (split analyses, only nonbiologic extracted).	NR	(73.7 (Concomitant)
ASSURE	ABT + cDMARDs	83.9% white	NR	Active disease (functional classes I, II, III, IV ACR) despite ≥1 biologic and/or nonbiologic therapy, stable dose for ≥28 days before trial (split analyses, only nonbiologic extracted).	NR	71.6 (Concomitant)
AUGUST II	MTX+PBO n=76		83	100%prior MTX	NR	59
AUGUST II	ADA+MTX n=79		81	100%prior MTX	NR	66
CHANGE	PBO n=87	NR	86.2	87.2% prior MTX [91.5 % 2 or more DMARDsacross all arms]	NR	NR
CHANGE	ADAmon n=91	NR	90.8	87.2% prior MTX	NR	NR
DE019	MTX+PBO n=200	83.0% white	89.5	100% prior MTX mean 2.4 prior cDMARDs including MTX	NR	49.5
DE019	ADA+MTX n=207	83.6% white	81.6	100% prior MTX mean 2.4 prior cDMARDs including MTX	NR	across two ADA arms, 44.9%
STAR	PBO+cDMARDs n=318	85.8% white	62.3	mean 1.2 prior cDMARDs	63.8	54.4
STAR	ADA+cDMARDs n=318	89.0% white	63.4	mean 112 prior cDMARDs	62.3	50.9
van de Putte	PBO s.c.	NR	81.8	Previous treatment with at least one DMARD	83.6	67.3

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
2004				had failed, with patients having active RA defined as ≥ 12 tender joints (0-68 scale), ≥ 10 swollen joints (0-66 scale), and either ESR ≥ 28 mm/1st h or CRP ≥ 20 mg/l. Patients excluded if had received investigational small molecule drug or biological agent within 2 months or 6 months before screening respectively. Four-week washout period required for patients taking cDMARDs at time of recruitment. Number of cDMARDs = 3.6 (1.8)		
van de Putte 2004	ADA mon	NR	79.6	Number of cDMARDs = 3.8 (1.8)	82.3	68.1
ARMADA	MTX+PBO (n=62)	NR	Rheumatoid factor, IU/litre mean(SD) 321.2 (518.2)	100% prior MTX mean 3.0 prior cDMARDs including MTX	NR	58.1
ARMADA	ADA+MTX (n=67)	NR	Rheumatoid factor, IU/litre mean(SD) 269.3 (390.0)	100% prior MTX mean 2.9 prior cDMARDs including MTX	NR	across all ADA dose arms 46.4%
Kim 2007	MTX+PBOrescueWeek18 n=65	NR	82.5	100%prior MTX 79.3% used 2 or 3 cDMARDs	NR	NR
Kim 2007	ADA+MTX n=63	NR	76.9	100%prior MTX 86.2% used 2 or 3 cDMARDs	NR	NR
CERTAIN	PBO + cDMARDs	NR	67.3	Inclusion criteria of using cDMARD therapy for ≥6 months (and <10 years). No prior anti-TNF use. [redacted]	NR	NR
CERTAIN	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + DMARDs	NR	74.0	Inclusion criteria of using cDMARD therapy for ≥6 months (and <10 years). No prior anti-TNF use. [redacted]	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
				[redacted]		
REALISTIC	PBO + existing cDMARDs	NR	NR overall trial pop 76.5	Inadequate response to ≥1 DMARD. Post-hoc analysis of those with DAS28 >5.1 at baseline, ≥2 prior cDMARDs and anti-TNF naïve.	NR	NR
REALISTIC	CTZ 400mg weeks 0, 2, 4 then 200mg every 2 weeks + existing cDMARDs	NR	NR overall trial pop 73.9	Inadequate response to ≥1 DMARD. Post-hoc analysis of those with DAS28 >5.1 at baseline, ≥2 prior cDMARDs and anti-TNF naïve.	NR	NR
ADORE	ETNmon n=159	White 158 (99.4%) Black 0 (0%) Asian 1 (0.6%)	70.9	100% prior MTX mean 2 .2 other prior DMARDs	74.2	51.6
ADORE	ETN+MTX n=155	White 153 (98.7%) Black 2 (1.3%) Asian 0 (0%)	69.5	100% prior MTX mean 2.3 other prior DMARDs	81.3	56.8
CREATEIIb	DMARD+PBO n=65	NR	81.5	100 % prior MTX or SSZ	NR	NR
CREATEIIb	ETN50+DMARD n=64	NR	85.9	100 % prior MTX or SSZ	NR	NR
ETN Study 309 (Combe 2006)	SSZ+PBO n=50	NR	NR	100%prior SSZ 58% prior cDMARDs other than SSZ	NR	40
ETN Study 309 (Combe 2006)	ETN+PBO n=103	NR	NR	100%prior SSZ 69.9% prior cDMARDs other than SSZ	NR	59.
ETN Study 309 (Combe 2006)	ETN+SSZ n=101	NR	NR	100%prior SSZ 58.4% prior cDMARDs other than SSZ	NR	44.6
JESMR	ETN 25mg Q2W monotherapy	NR	91.5	Non-response to MTX (6-8mg/week). No prior biologics.	NR	46.4
JESMR	ETN 25mg Q2W + MTX 6-8mg/week	NR	86.7	Non-response to MTX (6-8mg/week). No prior biologics.	NR	60.3
Lan 2004	PBO+MTX , n=29	NR	NR	100% prior MTX	NR	NR
Lan 2004	ETN+MTX ,			100% prior MTX	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
	n=29					
LARA	MTX+DMARD n=142	White, n (%)65 (45.8) Mestizos, n (%) 34 (23.9) African-Latin American, n (%)23 (16.2) Other, n (%) 20 (14.1)	83.8	100 prior MTX	NR	NR
LARA	ETN50+MTX n=281	White, n (%) 134 (47.7) Mestizos, n (%) 60 (21. African-Latin American, n (%) 39 (13.9) Other, n (%) 48 (17.1)	86.1	100 prior MTX		
Moreland 1999	PBO n=80	89% white	79	90%prior MTX mean 3 prior cDMARDs including MTX	84	58
Moreland 1999	ETN+PBO n=78	94% white	79	87%prior MTX mean 3.3 prior cDMARDs including MTX	67	81
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178	90.4% white	65.7	100% prior MTX	NR	47.2
RACAT (O'Dell 2013)	ETN50+MTX n=175	83.4% white	67.2	100% prior MTX		49.7
Wajdula 2000 [358]	PBO n=111			mean 3.5 prior cDMARDs failed to respond to at least one DMARD	85	71
Wajdula 2000	ETN			mean 3.6 prior cDMARDs failed to respond to at least one	86	70

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
	n=105			DMARD		
Weinblatt 1999	MTX plus placebo, n=30	White 83%	90	100 prior MTX	80	70
Weinblatt 1999	Etanercept 25mg twice weekly plus MTX, n=59	White 76%	84	100 prior MTX	75	53
APPEAL	MTX plus DMARD (SSZ, HCQ or leflunomide), n=103	NR	NR	100% prior MTX 30.1% also other cDMARD(S)	NR	NR
APPEAL	Etanercept 25mg twice weekly (licensed dose) plus MTX, n=197	NR	NR	100% prior MTX 24.4% also other cDMARD(S)	NR	NR
GO-FORTH	PBO Q4W + MTX 6-8mg/week	NR	NR	All patients had received MTX >6mg/week for ≥3 months prior to the start of the study. Other prior DMARDs and biologics not reported.	NR	NR
GO-FORTH	GOL 50mg s.c. Q4W + MTX 6-8mg/week	NR	NR	All patients had received MTX >6mg/week for ≥3 months prior to the start of the study. Other prior DMARDs and biologics not reported.	NR	NR
GO-FORWARD	PBO s.c. every 4 weeks + MTX	NR	81.2	Patients had to have been on stable MTX dose of 15mg/week or greater but 25mg/week or less during 4 week period immediately preceding screening. Must have tolerated at least 15 mg/week for at least 3 months before screening. Patients had active RA defined as ≥ 4 of 66 swollen joints, ≥ 4 of 68 tender joints, and at least 2 of following criteria: CRP ≥ 1.5 mg/dl or ESR ≥ 28 mm/h. Median (IQR) MTX dose (mg/week) = 15.0 (15.0 to 20.0) Duration of previous MTX use (years) < 1 = 33 (24.8%) ≥ 1 to < 3 = 30 (22.6%) ≥ 3 = 68 (51.1%) Patients with previous use of DMARD other than MTX = 94 (70.7%)	85.7%	65.4

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
				(Any previous use of any anti-TNF agent, rituximab, natalizumab or cytotoxic agents excluded patients from trial participation. In addition, patients should not have taken anakinra; DMARDs other than MTX; or i.v., i.m. or i.a. corticosteroids within 4 weeks before first dose of study drug or alefacept or efalizumab within 3 months of first dose of study drug)		
GO-FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	NR	86.5 (77/89)	Median (IQR) MTX dose (mg/week) = 15.0 (15.0 to 20.0) Duration of previous MTX use (years) < 1 = 20 (22.5%) ≥ 1 to < 3 = 32 (36.0%) ≥ 3 = 37 (41.6%) Patients with previous use of DMARD other than MTX = 70 (78.7%)	86.5%	75.3
Kay 2008 (NCT00207714)	PBO s.c. + MTX	NR	NR	All patients treated with MTX at dosage of at least 10 mg/week for ≥ 3 months and at stable dosage for ≥ 4 weeks before receiving first dose of study drug. Patients had active RA defined as ≥ 6 swollen joints, ≥ 6 tender joints and at least 2 of the following 3 criteria: CRP ≥ 1.5 mg/dl, ESR ≥ 28 mm/h or morning stiffness of ≥ 30 mins.	NR	NR
Kay 2008	GOL 50 mg s.c. every 4 weeks + MTX	NR	NR		NR	NR
Abe 2006	PBO + MTX	Japanese patients	NR	Eligible patients had received MTX treatment for more than 3 months, with a stable MTX dosage at 6 mg/week or more during the last 4 weeks. Patients had active RA defined as ≥ 6 of 68 tender joints, ≥ 6 of 66 swollen joints, and at least 2 of the	95.7	89.4

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
				following: morning stiffness ≥45 mins, ESR ≥28 mm/hr, or CRP ≥ 2 mg/dl.Patients not permitted to use DMARD, immunosuppressive drugs other than MTX, or i.a., i.m., i.v. or epidural corticosteroids		
Abe 2006	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 + MTX		NR		89.8	85.7
ATTRACT (Anti-TNF Trial in rheumatoid arthritis with Concomitant Therapy)	PBO i.v. + MTX	White 78/88 (89)	77	Patients had been receiving MTX for at least 3 months with no break in treatment of more than 2 weeks during that period. MTX dose required to have been stable at ≥ 12.5 mg/wk for at least 4 weeks before screening. Patients were excluded if they had used a DMARD other than MTX or received IA/IM /IV corticosteroids in 4 weeks before screening; received any other agent to reduce TNF. Mean number (SD) of previous DMARDs (excluding MTX) = 2.5 (1.4)	72	64
ATTRACT	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter +MTX	White 80/86 (93)	84	Mean number (SD) of previous DMARDs (excluding MTX) = 2.8 (1.5)	79	63
Durez 2004	Single i.v. infusion of methylprednisolone (sodium hemisuccinate) at week 0 + MTX	NR	87	Eligible patients had received 15 mg/wk MTX treatment (10 mg when tolerance poor). Previous treatment with i.v. MP pulse and/or anti-TNF agents excluded patients from participation. By randomisation, patients had received: MTX (100%), sulfasalazine (85%), gold salts (79%), hydroxychloroquine (61%), cyclosporine A (58%), D-penicillamine (42%), azathioprine (30%) and leflunomide (18%) (authors stated no differences between i.v. MP and IFX arms, no data presented). Previous DMARDs = Median 3 (range 1-7)	NR	NR
Durez 2004	IFX 3 mg/kg at weeks 0, 2 and 6 + MTX	NR	67	Previous DMARDs = Median 3 (range 2-6)	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
START	PBO + MTX	NR	80.7	All patients had been receiving MTX for at least 6 months prior to randomisation and were permitted to receive stable doses of the following: chloroquine, azathioprine, penicillamine, oral/intramuscular gold, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, oral corticosteroids, NSAIDs. No prior biologics allowed.	39.4	59
START	IFX 3mg/kg + MTX	NR	82.8	All patients had been receiving MTX for at least 6 months prior to randomisation and were permitted to receive stable doses of the following: chloroquine, azathioprine, penicillamine, oral/intramuscular gold, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, oral corticosteroids, NSAIDs. No prior biologics allowed.	43.3	59.2
Swefot	Sulfasalazine (1000 mg twice daily orally) + hydroxychloroquine (400 mg daily orally) + MTX	NR	65	Patients with early RA (with no previous treatment with DMARDs) were administered MTX (up to 20 mg/wk). After 3-4 months, patients who had not achieved low disease activity (having DAS28 > 3.but were able to tolerate MRX were randomised to treatment arms.	NR	8
Swefot	IFX 3 mg/kg i.v. at weeks 0, 2, 6 and every 8 weeks thereafter+MTX	NR	69		NR	6
Wong 2009	PBO + MTX (with crossover to open-label IFX at week 24).	NR	7/8	Eligible patients had failed on two DMARDs including MTX. All patients had been receiving MTX (≤ 25 mg/wk).	NR	NR
Wong 2009	IFX 3 mg/kg at weeks 0, 2, 6 and 8 weeks thereafter + MTX	NR	7/16		NR	NR
Zhang 2006	PBO i.v. + MTX	Chinese patients	NR	Patients had been treated with MTX for at least 3 months at a stable dose (7.5 to 20 mg/wk) for at least 4 weeks. Patients who began treatment with other DMARDs within 4 weeks before screening were ineligible. Treatment with other anti-TNF agents within 3 months of study entry was not permitted.	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
				64.0% had previously used drug other than MTX (no other details)		
Zhang 2006	IFX 3 mg/kg i.v. at weeks 0, 2, 6 and 14 + MTX		NR	55.2% had previously used drug other than MTX (no other details)	NR	NR
ACT-RAY (NCT00810199)	TCZ 8 mg/kg i.v. every 4 weeks + oral PBO (277 randomised)	NR	NR	Subjects had been receiving MTX for at least 12 weeks with stable dose of at least 15 mg/week for at least 6 weeks before starting study treatment. Patients were excluded if had any previous use of biological agents as well as any cDMARD drug treatment other than MTX during the month (3 months for leflunomide) preceding baseline visit. Mean MTX dose, mg/week (SD) = 16.2 (4.1) Number of prior DMARDs (including MTX before study entry), mean (SD) = 1.9 (1.0)	NR	49.1
ACT-RAY	TCZ 8 mg/kg i.v. every 4 weeks + MTX	NR	NR	Mean MTX dose, mg/week (SD) = 16.0 (4.4) Number of prior DMARDs (including MTX before study entry), mean (SD) = 1.9 (1.1)	NR	48.9
MEASURE	PBO + MTX	NR	NR	Patients were described as MTX inadequate responders	NR	NR
MEASURE	TCZ 8 mg/kg i.v. every 4 weeks + MTX	NR	NR		NR	NR
Nishimoto 2004	PBO i.v. every 4 weeks	NR	NR	Eligible patients had been treated unsuccessfully (due to lack of efficacy) with ≥ 1 DMARD or immunosuppressant. Active RA defined as ≥ 6 swollen joints, ≥ tender joints and 1 of following 2 criteria: ESR ≥ 30 mm/h or CRP > 1.0 mg/dl. No DMARDs permitted during 4 week washout period before initiation of study agent and during study period. No. of failed DMARDs (median (range))= 5 (1-	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
				10)		
Nishimoto 2004	TCZ 8mg/kg i.v. every 4 weeks	NR	NR	No. of failed DMARDs (median (range))= 5 (1-11)	NR	NR
SAMURAI	cDMARDsDiseaseActivity n=145	NR	NR	67% prior MTX	NR	NR
SAMURAI	TCZi.v. n=157	NR	NR	73% prior MTX	NR	NR
SATORI (NCT00144521)	PBO i.v. every 4 weeks + MTX	NR	NR	Mean number of failed DMARDs (range) = 3.6 (1 to 8) All candidates were treated with MTX 8 mg/week for at least 8 weeks until enrolment. Inadequate response to MTX defined as presence of active disease (as above). Patients not permitted to receive prior anti-TNF agents or leflunomide (within 12 weeks prior to first dose). Patients not permitted to receive DMARDs other than MTX or immunosuppressants (within 2 weeks prior to first dose))	NR	NR
SATORI	TCZ 8 mg/kg i.v. every 4 weeks+ PBO capsule	NR	NR	Mean number of failed DMARDs (range) = 3.3 (1 to 8)	NR	NR
TOWARD	PBO i.v. every 4 weeks + stable cDMARDs	72% White 10% Asian 8% American Indian/Native Alaskan 7% Black 3% Other	NR	Eligible patients had received stable doses of permitted DMARDs (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide) for ≥ 8 weeks before study entry. Patients unsuccessfully treated with an anti-TNF agent or any cell-depleting therapy were excluded. Medication at baseline (%): MTX = 73.9 Chloroquine/hydroxychloroquine = 19.8 Sulfasalazine = 14.3 Leflunomide = 15.5 Parenteral gold = 0.7	77.1	54.6

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	% receiving NSAIDs at baseline	% receiving steroids at baseline
				Azathioprine = 2.2 Number of background DMARDs at baseline (%): 1 = 75 2 or more = 24 None = 1		
TOWARD	TCZ 8 mg/kg i.v. every 4 weeks + stable DMARDs	72% White 9% Asian 10% American Indian/Native Alaskan 4% Black 3% Other	NR	Medication at baseline (%): MTX = 75.8 Chloroquine/hydroxychloroquine = 20.6 Sulfasalazine = 13.1 Leflunomide = 12.1 Parenteral gold = 0.2 Azathioprine = 2.2 Number of background DMARDs at baseline (%): 1 = 77 2 or more = 22 None = 1	71.4	51.2
[redacted] unpublished	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] unpublished	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Table 353: Population characteristics: Trials providing additional evidence for the NMA

Trial name / Author, year	Treatment arms for which data extraction performed	Mean Age (years, SD)	Gender (% female)	Early withdrawal plan reported?	Disease duration (years, SD)	Mean DAS28 score at baseline (SD) (ESR or CRP where stated)
ACQUIRE	ABT . + PBO + MTX n=736	49.9 (13.2)	84.4	NR	7.6 (8.1)	6.23 (0.85) (CRP)
ACQUIRE	ABT. + PBO. + MTX n=721	50.1 (12.6)	80.4		7.7 (7.8)	6.20 (0.8DAS-28 CRP
NCT00254293	PBO + MTX n=119	54.7 (NR) range 23-80	66	NR	8.9 (8.3)	5.5 (0.87) CRP
NCT00254293	ABT i.v. (~10mg/kg) + MTX n=115	55.8 (NR) range 17-83	75		9.7 (9.8)	5.5 (0.6CRP
ORAL STANDARD	MTX+PBO n=108	53.7	75.9	Yes	7.9	6.5 ESR 5.5CRP
ORAL STANDARD	TOF5+MTX n=204	53.0	85.3		7.6	6.6 ESR 5.4 CRP
ORAL STANDARD	TOF10+MTX n=201	52.9	83.6		7.4	6.5 ESR 5.4 CRP
ORAL STANDARD	ADA+MTX n=204	52.5	79.4		8.1	6.4 ESR 5.3 CRP
JRAPID	MTX + PBO n=77	51.9 (11.1)	85.7	Yes	5.8 (4.1)	6.5 (0.9) (ESR)
JRAPID	CTZ 200mg Q2W + MTX n=82	50.6 (11.4)	84.1		5.6 (4.2)	6.2 (0.8) (ESR)
RA0025	PBO + MTX n=40	51.6 (11.7)	88.9	Yes	6.5 (4.2)	7.33 (1.09) ESR
RA0025	CTZ + MTX n=81	50.8 (11.1)	87.5		5.5 (4.6)	7.46 (1.29) ESR
RAPID1	PBO + MTX n=199	52.2 (11.2)	83.9	Yes	6.2 (4.4)	7.0 (0.9) ESR
RAPID1	CTZ + MTX n=393	51.4 (11.6)	82.4		6.1 (4.2)	6.9 (0.8) ESR
RAPID2	PBO + MTX n=127	51.5 (11.8)	84.3	Yes	5.6 (3.9)	6.83 (0.87) ESR
RAPID2	CTZ + MTX n=246	52.2 (11.1)	83.7		6.1 (4.1)	6.85 (0.84) ESR
TEAR	MTXmon(ST) n=124 ST =step-up from MTX to triple	49.3	70.2	Yes	0.38	5.8 ESR

	disease-modifying antirheumatic drug therapy (MTX plus SSZ plus HCQ);					
TEAR	MTXmon(SE) n=255 SE=step-up from MTX to MTX plus etanercept;	48.6	69		0.24	5.8 ESR
TEAR	MTX+SSZ+HCQ n=132	48.8	76.5		0.34	5.8 ESR
TEAR	ETN50+MTX n=244	50.7	74.2		0.29	5.8 ESR
TEMPO	MTXmon n=228	53.0	79	NR	6·8 (5·5)	5.5 (1.2)
TEMPO	ETNmon n=223	53.2	77		6·3 (5·1)	5.7 (1.1)
TEMPO	ETN+MTX n=231	52.5	74		6·8 (5·4)	5.5 (1.2)
AMBITION (ITT baseline covariate data presented)	MTX n=284	50.0 (12.9)	79	NR	6.2 (7.8)	6.8 (0.9)
AMBITION	TCZ mon n=288	50.7 (13.1)	83		6.4 (7.9)	6.8 (1.0)
LITHE	PBO + MTX n=393	51.3 (12.4)	83	Yes	Mean (range) = 9.0 (0.5-44.3)	6.5 (1.0)
LITHE	TCZ + MTX n=398	53.4 (11.7)	82		Mean (range) = 9.3 (0.6-48.8)	6.6 (1.0)
OPTION	PBO + MTX n=204	50.6 (12.1)	78	NR	7.8 (7.2)	6.8 (0.9)
OPTION	TCZ + MTX n=205	50.8 (11.8)	85		7.5 (7.3)	6.8 (0.9)

Table 354: Population characteristics additional information NMA sensitivity analyses trials

Trial name / Author, year	Treatment arms for which data extraction performed	Ethnicity (where reported)	Rheumatoid factor (% positive)	Prior DMARD treatment history (brief description, including definition of active RA despite previous treatment, where relevant)	nN (%) receiving NSAIDs at baseline	nN (%) receiving steroids at baseline
ACQUIRE	ABT s.c. + PBO i.v. + MTX	74.7% Caucasian	84.8	Inadequate response to ≥3 months of MTX at ≥15mg/week. Prior biologics in 4.3% of the sample.	NR	NR
ACQUIRE	ABT i.v. + PBO s.c. + MTX	74.5% Caucasian	85.9	Inadequate response to ≥3 months of MTX at ≥15mg/week. Prior biologics in 6.0% of the sample.	NR	NR
NCT00254293	PBO + MTX	87% white	NR	99.2% prior MTX, 21.0% other prior DMARDs, 2.6% prior anti-TNF.	NR	67.2
NCT00254293	ABT i.v. (~10mg/kg) + MTX	87% white	NR	99.1% prior MTX, 16.5% other prior DMARDs, 2.6% prior anti-TNF.	NR	60.0
ORAL STANDARD	MTX+PBO	Region of origin North America 28.7% Latin America 4.7% Europe 49% Other 18.5%	66.3	100% prior MTX 54.7% other prior cDMARDs 8.3% prior TNFi	NR	66.7
ORAL STANDARD	TOF5+MTX	Region of origin North America 24.5% Latin America 3.9 Europe 53.9% Other 17.6%	66.8	100% prior MTX 53.4% other prior cDMARDs 5.9% prior TNFi	NR	61.8
ORAL STANDARD	TOF10+MTX	Region of origin North America 24.9% Latin America 1.5%	66.2	100% prior MTX 57.2% other prior cDMARDs 7.0% prior TNFi	NR	64.2

		Europe 55.7% Other 17.9%				
ORAL STANDARD	ADA+MTX	Region of origin North America 25.5% Latin America 2.9% Europe 53.9% Other 17.6%	68.2	100% prior MTX 55.9% other prior cDMARDs 7.8% prior TNFi	NR	61.3
Yamamoto 2011 / JRAPID (NCT00791999)	MTX + PBO	NR	85.7	Inadequate response to MTX . 19.5% had prior TNF inhibitors.	NR	NR
JRAPID	CTZ 200mg Q2W + MTX	NR	86.6	Inadequate response to MTX . 13.4% had prior TNF inhibitors.	NR	NR
RA0025	PBO + MTX	NR	NR	Inadequate response to MTX. Study MTX dose 10-20 mg (min-max). Prior TNF inhibitors in 13.6%.	NR	NR
RA0025	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + MTX	NR	NR	Inadequate response to MTX. Study MTX dose 10-20 mg (min-max). Prior TNF inhibitors in 17.5%.	NR	NR
RAPID1	PBO + MTX	NR	82.8	Patients were required to receive MTX for ≥6 months with a stable dosage of ≥10mg/week for ≥2 months prior to baseline. No biologics within 6 months of baseline (or within 3 months for ETN/ANA) and/or no previous biologics that resulted in severe hypersensitivity or anaphylactic reaction, or response failure to anti-TNF agent. Mean (SD) of 1.4 (1.previous DMARDs. Prior TNF inhibitors in 3.5%.	NR	NR
RAPID1	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + MTX	NR	79.6	Patients were required to receive MTX for ≥6 months with a stable dosage of ≥10mg/week for ≥2 months prior to baseline. No biologics within 6 months of baseline (or within 3 months for ETN/ANA) and/or no previous biologics that resulted in severe hypersensitivity or anaphylactic reaction, or response failure to anti-TNF agent. Mean (SD) of 1.3 (1.previous DMARDs. Prior TNF inhibitors in 2.8%.	NR	NR
RAPID2	PBO + MTX	NR	78.2	Patients were required to receive MTX for ≥6 months with a stable dosage of ≥10mg/week for ≥2 months prior to baseline. No biologics within 6 months of baseline (or within 3 months for ETN/ANA) and/or no previous biologics that resulted in severe hypersensitivity or anaphylactic reaction,	NR	59.8

				or response failure to anti-TNF agent. Mean (SD) of 1.2 (1.previous DMARDs excluding MTX. Prior anti-TNF use in 1.6% patients.		
RAPID2	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + MTX	NR	77.5	Patients were required to receive MTX for ≥6 months with a stable dosage of ≥10mg/week for ≥2 months prior to baseline. No biologics within 6 months of baseline (or within 3 months for ETN/ANA) and/or no previous biologics that resulted in severe hypersensitivity or anaphylactic reaction, or response failure to anti-TNF agent. Mean (SD) of 1.2 (1.previous DMARDs excluding MTX. Prior anti-TNF use in 1.6% patients.	NR	55.3
TEAR	MTXmon(ST) n=124 ST =step-up from MTX to triple disease-modifying antirheumatic drug therapy (MTX plus SSZ plus HCQ);	White 85.5% African American 11.3% Hispanic 8.1%	87.1	14.5% prior MTX 0% prior biologics	NR	33.1
TEAR	MTXmon(SE) n=255 SE=step-up from MTX to MTX plus etanercept;	White 78..4% African American 11.4% Hispanic 12.6%	91	20% prior biologics 0.8% prior MTX	NR	43.5
TEAR	MTX+SSZ+HCQ n=132	White 81.1% African American 8.3% Hispanic 12.9%	91.7	20.5% prior MTX 0% prior biologics	NR	43.9
TEAR	ETN50+MTX n=244	White 77.1% African American 12.7% Hispanic 10.7%	88.5	24.6% prior MTX 0.8% prior MTX	NR	43.0
TEMPO	MTXmon n=228	NR	71	42% prior MTX mean 2.3 prior cDMARDs including MTX	86	64

TEMPO	ETNmon n=223	NR	75	42% prior MTX mean 2.3 prior cDMARDs including MTX	88	57
TEMPO	ETN+MTX n=231	NR	76	44% prior MTX mean 2.3 prior cDMARDs including MTX	88	62
AMBITION (ITT baseline covariate data presented)	MTX alone	NR	NR	Patients excluded if had been unsuccessfully treated with an anti-TNF agent, had received MTX in the 6 months before randomisation or discontinued MTX due to clinically important adverse effects or lack of efficacy. Patients who had temporarily discontinued MTX due to side effects or desire to become pregnant and those who discontinued anti-TNF agents for reasons other than efficacy (e.g. treatment cost, side effects) could participate in study. Patients had active RA defined as ≥ 6 of 66 swollen joints, ≥ 8 of 68 tender joints, and CRP ≥ 1 mg/dl or ESR ≥ 28 mm/hr. MTX-naïve = 67% No. previous DMARDs / anti-TNF agents, mean (SD) = 1.1 (1.4) Previous use of anti-TNF agents = 7.4% (PP)	NR	47
AMBITION	TCZ 8mg/kg i.v. every 4 weeks	NR	NR	MTX-naïve = 67% No. previous DMARDs / anti-TNF agents, mean (SD) = 1.2 (1.3) Previous use of anti-TNF agents = 8.3% (PP)	NR	48
LITHE	PBO i.v. every 4 weeks + MTX	NR	82	Eligible patients had inadequate responses to MTX (despite receiving MTX for ≥ 12 weeks before baseline (stable dose of 10-25 mg/wk for ≥ 8 weeks)), with active RA defined as ≥ 6 swollen joints, ≥ 8 tender joints, and either CRP ≥ 1 mg/dl or ESR ≥ 28 mm/hr, and had ≥ radiographically confirmed joint erosion. All other DMARDs or biological agents were discontinued before study entry (LEF for ≥ 12 weeks, IFX or ADA for ≥ 8 weeks and ETN for ≥ 2 weeks). Additional exclusion criteria: failure to respond to anti-TNF treatment. No. of previous DMARDs/anti-TNFs, mean (SD) = 1.6 (1.5) % with past use of DMARDs = 71.2 % with past use of anti-TNF agents = 11.5	NR	70

LITHE	TCZ 8 mg/kg i.v. every 4 weeks + MTX	NR	83	No. of previous DMARDs/anti-TNFs, mean (SD) = 1.6 (1.4) % with past use of DMARDs = 75.4 % with past use of anti-TNF agents = 10.8	NR	62
OPTION	PBO i.v. every 4 weeks + MTX	NR	71	Eligible patients had experienced an inadequate response to MTX, with active RA defined as ≥ 6 swollen joints, ≥ 8 tender joints and CRP ≥ 10 mg/l or ESR ≥ 28 mm/hr. Patients had received MTX for ≥ 12 weeks before study entry (with a stable dose of 10-25 mg/week for ≥ 8 weeks). All other DMARDs were discontinued prior to study entry (LEF for ≥ 12 weeks, AKR for ≥ 1 week, ETN for ≥ 2 weeks, and IFX or ADA for ≥ 8 weeks). Patients excluded if had previous unsuccessful anti-TNF treatment (discontinuations due to cost or injection discomfort not excluded). No. of previous DMARDs (not including MTX) = 1.7 (1.5) Previous anti-TNF treatment = 19/204 (5%)	68	54
OPTION	TCZ 8 mg/kg i.v. every 4 weeks + MTX	NR	83	No. of previous DMARDs (not including MTX) = 1.5 (1.4) Previous anti-TNF treatment = 11/205 (5%)	66	55

Table 355: DAS Population 1 Head to head trial

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	DAS28 mean change from baseline (SD)
Kume 2011 [90]	ADA mon	24 weeks	DAS28-ESR	19	5.34 (1.4) (n=21)	-2.12 (0.38)
Kume 2011	ETN mon	24 weeks	DAS28-ESR	20	5.17 (1.5) (n=21)	-2.84 (0.42)

Table 356: DAS Population 1 biologics vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% achieving DAS28 remission (defined threshold)
GUEPARD[83]	Initial MTX	week 12	NR	32	DAS28(ESR) 6.15 (SD0.88) DAS28(CRP) 5.85 (SD0.9)	NR	NR	DAS<2.6 12.5%
GUEPARD	Initial ADA+MTX	week 12	NR	33	DAS28(ESR) 6.31 (SD0.78) DAS28(CRP) 5.80 (SD0.8)	NR	NR	DAS<2.6 36.4%
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	week 52	NR	32	NR	NR	NR	DAS<2.6 59.4%
GUEPARD	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28	week 52	NR	33	NR	NR	NR	DAS<2.6 39.4%
HIT HARD[84] Ref MS as well as primary ref	MTX + PBO	24 weeks (study RCT endpoint)	DAS28-ESR	85	6.3 (0.9)	3.6 (1.4)	-2.7 (NR)	29.5 (<2.6)
HIT HARD	ADA + MTX	24 weeks (study RCT endpoint)	DAS28-ESR	87	6.2 (0.8)	3.0 (1.2) [a]	-3.2 (NR)	47.9 [a] (<2.6)
OPERA [97]	MTX + PBO + steroid	12 months (primary endpoint and study RCT endpoint)	DAS28-CRP	91	5.6 (3.8-7.0) [c]	2.6 (1.7-4.7) [c]	NR	49 (<2.6)
OPERA [97]	ADA + MTX + steroid	12 months (primary endpoint and study RCT endpoint)	DAS28-CRP	89	5.5 (3.8-7.8) [c]	2.0 (1.7-5.0) [a,c]	NR	74 [b] (<2.6)
OPTIMA [181]	MTX + PBO	26 weeks (study RCT endpoint)	DAS28-CRP	517	6.0 (.0	4.1 (n=505)	-1.9 (NR)	17 (<2.6)
OPTIMA	ADA + MTX	26 weeks (study RCT endpoint)	DAS28-CRP	515	6.0 (1.0)	3.3 [a] (n=499)	-2.7 (NR)	34 (<2.6) [b]
PREMIER	MTX + PBO	1 year (primary	NR	257	6.3 (0.9)	NR	NR	21 (<2.6)

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% achieving DAS28 remission (defined threshold)
		endpoint)						
PREMIER	ADA monotherapy + PBO step up week 16	1 year (primary endpoint)	NR	274	6.4 (0.9)	NR	NR	23 (<2.6)
PREMIER	ADA + MTX step up week 16	1 year (primary endpoint)	NR	268	6.3 (0.9)	NR	NR	43 (<2.6) [b (vs. MTX, vs. ADA)]
PREMIER	MTX + PBO	2 years (study RCT endpoint)	NR	257	6.3 (0.9)	NR	NR	25 (<2.6)
PREMIER	ADA monotherapy + PBO step up week 16	2 years (study RCT endpoint)	NR	274	6.4 (0.9)	NR	NR	25 (<2.6)
PREMIER	ADA + MTX step up week 16	2 years (study RCT endpoint)	NR	268	6.3 (0.9)	NR	NR	49 (<2.6) [b (vs. MTX, vs. ADA)]
COMET	MTX +PBO n=268	52 weeks	NR	263	6.5 (SD1.0)	NR	NR	DAS28<2.6 28%
COMET	ETN+MTX n=274	52 weeks	NR	265	6.5 (SD1.0)	NR	NR	DAS28<2.6 50% [b]
COMET [135]	MTX in year 1 MTX in year 2 n=99 at start of period 2	2 years	NR	130	NR	NR	NR	22%
COMET	MTX year 1 ETN+MTX in year 2 n=90 at start of period 2	2 years	NR	133	NR	NR	NR	36% [a] vs group given MTX both years
COMET	ETN+MTX in year 1 ETN+MTX in year 2 n=111 at start of period 2	2 years	NR	131	NR	NR	NR	45% [b] vs group given MTX both years
COMET	ETN+MTX in year 1 ETN in year 2 n=111 at start of period 2	2 years	NR	134	NR	NR	NR	37% [a] vs group given MTX both years
GO-BEFORE	PBO + MTX	24 weeks	DAS28-ESR	160	DAS28ESR= 6.2 (1.17)	NR	NR	DAS28-ESR 11
GO-BEFORE	GOL 50 mg s.c.	24 weeks		159	DAS28ESR= 6.3	NR	NR	25 [b]

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% achieving DAS28 remission (defined threshold)
	every 4 weeks + MTX				(1.1			
GO-BEFORE [136]	PBO + MTX	52 weeks	DAS28-CRP	160	DAS28ESR= 6.2 (1.17)	NR	NR	38.8
GO-BEFORE	GOL 50 mg s.c. every 4 weeks + MTX	52 weeks		159	DAS28ESR= 6.3 (1.1)	NR	NR	45
ASPIRE	PBO i.v. + MTX	54 weeks	NR	235	6.7 (1)	4.6 (1.8)	NR	(defined as DAS28 <2.6) 15.0
ASPIRE	IFX i.v. 3 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter + MTX	54 weeks	NR	294	6.6 (1)	4.0 (1.8) [b]	NR	21.2
BeST	Sequential monotherapy (DAS-steered)	6 months	DAS44	126	DAS44 = 4.5 (0.9)	3	NR	NR
BeST	Step-up combination therapy (DAS-steered)	6 months	DAS44	121	DAS44 = 4.5 (0.8)	3	NR	NR
BeST	Initial combination therapy with prednisone (DAS-steered)	6 months	DAS44	133	DAS44 = 4.4 (0.9)	2.2	NR	NR
BeST	Initial combination therapy with IFX (DAS-steered)	6 months	DAS44	128	DAS44 = 4.3 (0.9)	2.2	NR	NR
Durez 2007	MTX	52 weeks (study RCT endpoint)	DAS28-CRP	14	5.2 (0.8)	3.26 (1.3)	NR	NR
Durez 2007	MTX + i.v. methylprednisolone (MP)	52 weeks (study RCT endpoint)	DAS28-CRP	15	5.3 (1)	2.77 (1.09)	NR	NR
Durez 2007	IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22, 30, 46+MTX	52 weeks (study RCT endpoint)	DAS28-CRP	15	5.3 (1)	2.79 (0.77)	NR	NR
IDEA	MP 250 mg i.v. at week 0, PBO i.v. at weeks 2, 6, 14, 22 + MTX	26 weeks	NR	56	NR	NR	NR	(DAS (assumed DAS4 < 1.6) 44.6
IDEA	IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22 + MTX (IFX dose modifications	26 weeks	NR	54	NR	NR	NR	33.3

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% achieving DAS28 remission (defined threshold)
	permitted according to DAS44 from week 26)							
Quinn 2005	MTX + PBO	14 weeks (primary endpoint)	Not stated	10	7.0 (0.9)	6.0 (4.9-6.8) [d,e]	NR	NR
Quinn 2005	IFX 3mg/kg + MTX	14 weeks (primary endpoint)	Not stated	10	6.2 (0.8)	2.9 (2.3-3.8) [a,d,e]	NR	NR
Quinn 2005	MTX + PBO	54 weeks (study RCT endpoint)	Not stated	10	7.0 (0.9)	4.6 (3.1-5.1) [d,e]	NR	NR
Quinn 2005	IFX 3mg/kg + MTX	54 weeks (study RCT endpoint)	Not stated	10	6.2 (0.8)	Median (IQR): 2.7 (2.0-3.5) [d,e]	NR	NR

[a] = $p<0.05$
[b] = $p<0.01$
[c] = Median (5th, 95th centile range)
[d] = Median (IQR)
[e] = Estimated from graphical data

Table 357: DAS Population 2/3 Head to head

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% achieving DAS28 remission (defined threshold)
ATTEST[66]	PBO+MTX	Day 197	DAS28-ESR	110	6.8 (1.0)	NR	- 1.48	(defined as DAS28-ESR<2.6) 2.9
ATTEST[66]	IFX + MTX	Day 197	DAS28-ESR	165	6.8 (0.9)	NR	- 2.25 [b]	12.8
ATTEST[66]	ABT + MTX	Day 197	DAS28-ESR	156	6.9 (1.0)	NR	- 2.53 [b]	11.3
AMPLE	ABT s.c.	1 year (primary endpoint)	DAS28-CRP	318	5.5 (1)	3.188	-2.30 (0.08)	43.3 (<2.6)
AMPLE	ADA	1 year (primary endpoint)	DAS28-CRP	328	5.5 (1)	3.188	-2.27 (0.08)	41.9 (<2.6)
RED-SEA[104]	ADA+cDMARDs(REDSEA) n=60	24weeks	DAS28-CRP	60	5.6(0.9)	4.16(NR)	NR	NR
RED-SEA	ETN50+cDMARDs(REDSEA) n=60	24weeks	DAS28-CRP	60	5.8(0.9)	4.04(NR)	NR	NR
RED-SEA [136]	ADA+cDMARDs(REDSEA) n=60	12months	DAS28-CRP	60	NR	4.4 (3.1–5.0) [c]	-1.54(1.47)	NR
RED-SEA	ETN50+cDMARDs(REDSEA) n=60	12months	DAS28-CRP	60	NR	4.6 (3.5–5.6) [c]	-1.34 (1.3	NR
ADACTA	TCZ 8 mg/kg i.v. every 4 weeks + s.c. PBO ADA	24 weeks	DAS28-ESR	163	6.7 (0.9)	NR	- 3.3	(DAS28<2.6) 65/163 (39.9%)
ADACTA[55]	ADA 40 mg s.c. every 2 weeks + i.v. PBO TCZ	24 weeks	DAS28-ESR	162	6.8 (0.9)	NR	- 1.8 [b]	17/162 (10.5%) [b]

[a] = p<0.05
[b] = p<0.01
[c] = Median (IQR)

Table 358: DAS Population 2/3 biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% change from baseline	% achieving DAS28 remission (defined threshold)
AIM	MTX+PBO n=219	12 months	CRP	219	6.4 (0.1 CRP	NR	NR	NR	DAS28<3.2 9.9% DAS28<2.6 1.9%
AIM	ABTi.v.+ MTX n=433	12 months	CRP	433	6.4 (0.08) CRP	NR	NR	NR	DAS28<3.2 42.5% DAS28<2.6 23.8% [a]
ASSET	PBO + MTX	4 months (primary endpoint and study RCT endpoint)	DAS28-CRP	22	5.3 (0.9)	NR	-0.55 (95% CI -0.95, -0.16)	NR	0.0 (<2.6)
ASSET	ABT i.v. (~10mg/kg) + MTX	4 months (primary endpoint and study RCT endpoint)	DAS28-CRP	26	5.3 (1)	NR	-1.68 (95% CI -2.15, -1.2)	NR	15.4 (<2.6)
van de Putte 2004	PBO s.c.	26 weeks	NR	110	7.1 (0.9)	NR	- 0.7 (1.	- 9.1	NR
van de Putte 2004	ADA 40mg s.c. eow monotherapy	26 weeks	NR	113	7.1 (0.8)	NR	- 1.7 (1.6)	- 23.8 [b]	NR
CERTAIN	PBO + cDMARDs	24 weeks (primary endpoint and study RCT endpoint)	DAS28-ESR	98	4.47 (0.3	4.5	-0.07 (1.20)	NR	5.5 (<2.6)
CERTAIN	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + DMARDs	24 weeks (primary endpoint and study RCT endpoint)	DAS28-ESR	96	4.53 (0.4	3.38	-1.12 (1.06)	NR	26.1 (<2.6)
REALISTIC	PBO + existing cDMARDs	12 weeks	DAS28-CRP DAS28-ESR	29	NR	NR	-0.80 [e] -0.80 [e]	NR	NR
REALISTIC	CTZ 400mg weeks 0, 2, 4 then 200mg every 2 weeks + existing cDMARDs	12 weeks	DAS28-CRP DAS28-ESR	134	NR	NR	-1.88 [e] -1.94 [e]	NR	NR
ADORE	ETNmon n=159	16 weeks	ESR	156	6.2 ESR	NR	1.95	NR	DAS28 (4)<2.6 14.6% DAS28 (3) <2.6 15.2% [d]
ADORE	ETN+MTX n=155	16 weeks	ESR	151	6.3 ESR	NR	2.20	NR	DAS28 (4) <2.6 17.3% DAS28 (3) <2.6 15.1%

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% change from baseline	% achieving DAS28 remission (defined threshold)
CREATEIIb	DMARD+PBO	24 weeks	NR	65	6.3 (0.76)	NR	-1 (1.2)	NR	NR
CREATEIIb	ETN50+DMARD	24 weeks		64	6.4 (0.85)	NR	-2.3 (1.38)	NR	NR
JESMR	ETN 25mg Q2W monotherapy	24 weeks (primary endpoint)	Not stated	69	6.1 (CI: 5.9-6.)	4.1 (CI: 3.8-4.5)	NR	NR	10.1 (<2.6)
JESMR	ETN 25mg Q2W + MTX 6-8mg/week	24 weeks (primary endpoint)	Not stated	73	6.0 (CI: 5.8-6.)	3.3 (CI: 3.0-3.5) [b]	NR	NR	27.4 [a] (<2.6)
JESMR	ETN 25mg Q2W monotherapy	52 weeks (primary endpoint)	Not stated	69	6.1 (0.9)	4.2 (1.5)	NR	NR	18.8 (<2.6)
JESMR	ETN 25mg Q2W + MTX 6-8mg/week	52 weeks (primary endpoint)	Not stated	73	6.0 (1.0)	3.0 (1.0) [b]	NR	NR	35.6 [b] (<2.6)
LARA	MTX+DMARD(LARA)	24weeks	ESR	142	5.9(0.7)	NR	NR	NR	DAS<2.6 5/142 (3.5%) DAS<3.2 12.0%
LARA	ETN50+MTX	24 weeks		279	5.9(0.6)	NR	NR	NR	DAS<2.6 70/279 (25.1%) [b] DAS<3.2 47.0% [b]
RACAT (O'Dell 201	MTX+SSZ+HCQ	24weeks	CRP	157	5.8(0.9)	4.1(NR)	-1.79(1.20)	NR	DAS28≤2.6 12.7% DAS28≤3.2 24.8%
RACAT (O'Dell 2013)	ETN50+MTX	24 weeks		161	5.9(0.9)	3.8(NR)	-2.06(1.35)	NR	DAS28≤2.6 21.7% [a] DAS28≤3.2 34.8% [a]
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178 In analysis n=154 (of whom 39 switched to ETN)	48 weeks	CRP	154	NR	NR	-2.12(1.28)	NR	DAS28≤2.6 20.8% DAS28≤3.2 37.0%
RACAT (O'Dell 2013)	ETN50+MTX n=175 In analysis n=155 (of whom	48 weeks		155	NR	NR	-2.29(1.30)	NR	DAS28≤2.6 25.2%

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% change from baseline	% achieving DAS28 remission (defined threshold)
	41 switched to MTX+SSZ+HCQ)								DAS28≤3.2 41.9%
APPEAL	MTX plus DMARD (SSZ, HCQ or leflunomide)	16 weeks (primary endpoint and study RCT endpoint)	DAS28-ESR, DAS28-CRP	103	6.1 (1., 5.34 (1.	4.4, 3.7	NR	27.5, 31.0	7.8 (<0.26), 21.4 (<0.26)
APPEAL	Etanercept 25mg twice weekly (licensed dose) plus MTX	16 weeks (primary endpoint and study RCT endpoint)	DAS28-ESR, DAS28-CRP	197	6.1 (1., 5.23 (1.	3.8, [b] 3.1 [b]	NR	38.3, [b] 40.3 [b]	15.7 (<0.26), 41.6 [b] (<0.26)
GO-FORTH	PBO Q4W + MTX 6-8mg/week	14 weeks (primary endpoint)	DAS28-ESR	88	5.6 (0.99)	NR	-0.43 (1.20)	NR	3.4 (<2.6)
GO-FORTH	GOL 50mg s.c. Q4W + MTX 6-8mg/week	14 weeks (primary endpoint)	DAS28-ESR	86	5.5 (1.18)	NR	-1.98 (1.25) [b]	NR	31.4 [b] (<2.6)
GO-FORTH	PBO Q4W + MTX 6-8mg/week	24 weeks (study RCT endpoint)	DAS28-ESR	88	5.6 (0.99)	NR	-0.60 (1.38)	NR	6.8 (<2.6)
GO-FORTH	GOL 50mg s.c. Q4W + MTX 6-8mg/week	24 weeks (study RCT endpoint)	DAS28-ESR	86	5.5 (1.18)	NR	-2.05 (1.23) [b]	NR	34.9 [b] (<2.6)
GO-FORWARD	PBO s.c. every 4 weeks + MTX	14 weeks	DAS28-CRP DAS28-ESR	133	DAS28-CRP 5.458 (4.672 to 6.09) [c] DAS28-ESR 6.111 (5.260 to 6.57 [c]	NR	NR	NR	1.5
GO-FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	14 weeks	DAS28-CRP DAS28-ESR	89	DAS28-CRP 5.766 (4.628 to 6.32 [c] DAS28-ESR 6.105 (5.366 to 6.940) [c]	NR	NR	NR	15.7 [b]
GO-FORWARD	PBO s.c. every 4 weeks + MTX	24 weeks	DAS28-CRP DAS28-ESR	133	5.458 (4.672 to 6.09 [c] Median (IQR) = 6.111 (5.260 to 6.57 [c]	NR	NR	NR	6.0
GO-FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	24 weeks	DAS28-CRP DAS28-ESR	89	5.766 (4.628 to 6.32 [c] DAS28-ESR 6.105 (5.366 to 6.940) [c]	NR	NR	NR	20.2

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% change from baseline	% achieving DAS28 remission (defined threshold)
Kay 2008	PBO s.c. + MTX	16 weeks	Both measures reported	35	DAS28-CRP = 5.8 (5.2, 6.0) [c] DAS28-ESR = 6.3 (5.7, 7.0) [c]	NR	DAS28-CRP - 1.0 (1.0) - 1.0 (- 1.8, - 0.) [c] DAS28-ESR - 1.0 (1.) - 1.0 (- 2.0, 0.0)) [c]	NR	DAS28-CRP = 0 (DAS28 <2.6) DAS28-ESR = 0 (DAS28 <2.6)
Kay 2008	GOL 50 mg s.c. every 4 weeks + MTX	16 weeks	Both measures reported	35	DAS28-CRP = 5.9 (5.5, 6.9) [c] DAS28-ESR = 6.4 (5.6, 7.) [c]	NR	DAS28-CRP - 2.0 (1. (- 2.0 (- 2.6, - 1.5) [c] DAS28-ESR - 2.1 (1. - 2.2 (- 2.8, - 1.5) [c b]	NR	DAS28-CRP 11 [ca] (DAS28 <2.6) DAS28-ESR 5.7 (DAS28 <2.6)
START	PBO + MTX	22 weeks (primary endpoint and study RCT endpoint)	Not stated	363	NR	4.4 (1.40)	NR	NR	14 (<2.6)
START	IFX 3mg/kg + MTX	22 weeks (primary endpoint and study RCT endpoint)	Not stated	360	NR	3.5 (1.4) [b]	NR	NR	31 [b] (<2.6)
Wong 2009	PBO + MTX (with crossover for PBO group to open-label IFX at week 2.	Week 16	NR	NR	6.4 (0.8)	6.7	NR	NR	NR
Wong 2009	IFX 3 mg/kg at weeks 0, 2, 6 and 8 weeks thereafter + MTX	Week 16	NR	NR	6.2 (0.9)	4.4 [b]	NR	NR	NR
ACT-RAY	TCZ + oral PBO	24 weeks	DAS28-ESR	267	6.36 (1.00)	NR	- 3.21 (1.3)	NR	34.8%
ACT-RAY	TCZ + MTX	24 weeks	DAS28-ESR	277	6.33 (0.98)	NR	- 3.43 (1.3) [a]	NR	40.4% (P=0.19 for absolute difference of 5.65%, 95%CI -2.41, 13.71%)
ACT RAY	TCZ + oral PBO	52 weeks	NR	NR	6.36 (1.00)	NR	- 3.74	NR	36.6

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	DAS28-ESR or DAS28-CRP where stated	N analysed	Mean DAS28 score at baseline (SD)	Mean DAS28 score at follow-up (SD)	DAS28 mean change from baseline (SD)	% change from baseline	% achieving DAS28 remission (defined threshold)
ACT RAY	TCZ + MTX	52 weeks	NR	NR	6.33 (0.98)	NR	- 3.66	NR	45.5 [a]
MEASURE	PBO + MTX	12 weeks	NR	NR	NR	NR	- 0.8	NR	NR
MEASURE	TCZ + MTX	12 weeks	NR	NR	NR	NR	- 2.7	NR	NR
SAMURAI	cDMARDsDiseaseActivity	24weeks	NR	145	6.4(0.9)	5.91(nr)	NR	NR	NR
SAMURAI	TCZmon	24weeks	NR	157	6.5(08)	2.75(NR)	NR	NR	NR
SAMURAI	cDMARDsDiseaseActivity	52weeks	NR	145	NR	NR	NR	NR	DAS28<2.6 3%
SAMURAI	TCZmon	52weeks	NR	157	NR	NR	NR	NR	DAS28<2.6 59% [b]
SATORI	PBO i.v. every 4 weeks + MTX	24 weeks	NR	64	6.2 (0.9)	5.13 (SD NR)	NR	NR	NR
SATORI	TCZ 8 mg/kg i.v. every 4 weeks+ PBO capsules	24 weeks	NR	61	6.1 (0.9)	2.86 (SD NR)	NR	NR	NR
TOWARD	PBO i.v. every 4 weeks + stable cDMARDs (415 randomised)	24 weeks	NR	413	6.6 (1.0)	NR	- 1.16	NR	(DAS28 <2.6) 3
TOWARD	TCZ 8 mg/kg i.v. every 4 weeks + stable DMARDs (805 randomised)	24 weeks	NR	803	6.7 (1.0)	NR	- 3.17 [b]	NR	30 [b]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]									

[a] = p<0.05
[b] = p<0.01
[c] = Median (IQR):
[d] = The DAS28 (4) score is a function of ESR, the patient's Visual Analogue Scale of General Health (GH VAS), and the number of tender and swollen joints assessed using the 28-joint count method DAS28 (3) score, is a function of ESR, tender joint count and swollen joint count, but not GH VAS
[e] = least square

Table 359: HAQ-DI Population 1 trials, biologic vs. cDMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
GUEPARD[83]	Initial MTX	week 12	32	1.41 (0.74)	NR	-0.51; 95% CI -0.30, -0.72)	NR
GUEPARD	Initial ADA+MTX	week 12	33	1.69 (0.59)	NR	-0.82; 95% CI -0.52, -1.11	NR
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	week 52	32	NR	NR	-0.93 (95% CI -0.69,-1.17),	NR
GUEPARD	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28	week 52	33	NR	NR	-1.02 (95% CI -0.81, -1.24);	NR
HIT HARD[84]	MTX + PBO	24 weeks (study RCT endpoint)	85	1.3 (0.6)	0.72 (0.6)	-0.58 (NR)	NR
HIT HARD	ADA + MTX	24 weeks (study RCT endpoint)	87	1.4 (0.6)	0.49 (0.6)	-0.91 (NR)	NR
OPERA [97]	MTX + PBO + steroid	12 months (primary endpoint and study RCT endpoint)	91	1.00 (0.25-2.31) [c]	0.13 (0-1.5) [c]	-0.63 (-0.82-0.38)	NR
OPERA [97]	ADA + MTX + steroid	12 months (primary endpoint and study RCT endpoint)	89	1.13 (0.17-2.58) [c]	0.25 (0-1.44) [c]	-0.88 (-2.46-0.13)	NR
OPTIMA	MTX + PBO	26 weeks (study RCT endpoint)	517	1.6 (0.65)	0.9	-0.66 (0.73) (n=512)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
OPTIMA	ADA + MTX	26 weeks (study RCT endpoint)	515	1.61 (0.69)	0.7	-0.89 (0.74) (n=512)	NR
PREMIER	MTX + PBO	1 year (primary endpoint)	256	1.5 (0.7)	0.7 (0.6)	-0.8 (0.6)	NR
PREMIER	ADA monotherapy + PBO step up week 16	1 year (primary endpoint)	272	1.6 (0.6)	0.8 (0.6)	-0.8 (0.7)	NR
PREMIER	ADA + MTX step up week 16	1 year (primary endpoint)	266	1.5 (0.6)	0.5 (0.5)	-1.1 (0.6)	NR
PREMIER	MTX + PBO	2 years (study RCT endpoint)	256	1.5 (0.7)	0.5 (0.6)	-0.9 (0.6)	NR
PREMIER	ADA monotherapy + PBO step up week 16	2 years (study RCT endpoint)	272	1.6 (0.6)	0.6 (0.6)	-0.9 (0.7)	NR
PREMIER	ADA + MTX step up week 16	2 years (study RCT endpoint)	266	1.5 (0.6)	0.3 (0.5)	-1.0 (0.6)	NR
COMET	MTX +PBO	week 52	263	1.64 (0.65)	0.92 (0.74)	-0.72	NR
COMET	ETN+MTX	week 52	265	1.70 (0.68)	0.68 (0.71)	-1.02 [b]	NR
COMET [135]	MTX in year 1 MTX in year 2 n=99 at start of period 2	from week 52 to week 104	99	NR	NR	Non-significant change from baseline	NR
COMET	MTX year 1 ETN+MTX in year 2 n=90 at start of period 2	from week 52 to week 104	90	NR	NR	0.17(0.42) [b]	NR
COMET	ETN+MTX in year 1	from week 52 to week 104	111	NR	NR	Non-significant	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
	ETN+MTX in year 2 n=111 at start of period 2					change from baseline	
COMET	ETN+MTX in year 1 ETN in year 2 n=111 at start of period 2	from week 52 to week 104	111	NR	NR	Non-significant change from baseline	NR
ERA, Bathon 2000 Multicentre	MTX + PBO	12 months (study RCT endpoint)	217	NR	NR	-0.76 (SE=0.05)	NR
ERA, Bathon 2000 Multicentre	ETN 25mg Q2W + PBO	12 months (study RCT endpoint)	207	NR	NR	-0.73 (SE=0.05)	NR
GO-BEFORE	PBO + MTX	24 weeks	160	1.5 (0.64)	NR	NR	36.95
GO-BEFORE	GOL 50 mg s.c. every 4 weeks + MTX	24 weeks	159	1.5 (0.66)	NR	NR	43.65
ASPIRE	PBO i.v. + MTX	54 weeks	274	HAQ = 1.5 (0.6)	NR	HAQ 0.68 (0.63)	NR
ASPIRE	IFX i.v. 3 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter + MTX	54 weeks	351	HAQ = 1.5 (0.7)	NR	HAQ 0.80 (0.65)	NR
BeST	Sequential monotherapy (DAS-steered)	6 months	NR	Dutch-HAQ (0-3)=1.4 (0.7)	Dutch-HAQ (0-3)=0.9 (0.7)	NR	NR
BeST	Step-up combination therapy (DAS-steered)	6 months	NR	Dutch-HAQ= 1.4 (0.6)	0.9 (0.7)	NR	NR
BeST	Initial combination therapy with prednisone	6 months	NR	Dutch-HAQ= 1.4 (0.7)	0.5 (0.5)	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
	(DAS-steered)						
BeST	Initial combination therapy with IFX (DAS-steered)	6 months	NR	Dutch-HAQ= 1.4 (0.7)	0.5 (0.5)	NR	NR

95%CI = 95% confidence interval
SE = standard error

[a] = $p<0.05$
[b] = $p<0.01$
[c] = Median (5th, 95th centile range)

Table 360: HAQ-DI Population 2/3 Head-to-head trials

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
ATTEST[66]	PBO+MTX	Day 197	110	1.8 (0.7)	NR	NR	% achieving ≥0.3 improvement from baseline = 40.9
ATTEST[66]	IFX + MTX	Day 197	165	1.7 (0.7)	NR	NR	% achieving ≥0.3 improvement from baseline = 58.8 [a vs PBO+MTX]
ATTEST[66]	ABT + MTX	Day 197	156	1.8 (0.6)	NR	NR	% achieving ≥0.3 improvement from baseline = 61.5 [a vs PBO + MTX]
AMPLE	ABT s.c.	1 year (primary endpoint)	318	1.5 (0.7)	NR	NR	41.7
AMPLE	ADA	1 year (primary endpoint)	328	1.5 (0.7)	NR	NR	38.7
ADACTA[55]	TCZ 8 mg/kg i.v. every 4 weeks + s.c. PBO ADA	24 weeks	163	1.6 (0.6)	NR	- 0.7	NR
ADACTA[55]	ADA 40 mg s.c. every 2 weeks + i.v. PBO TCZ	24 weeks	162	1.7 (0.6)	NR	- 0.5	NR
DeFilippis 2006	ETN + MTX	22 weeks	16	1.89 (0.65)	NR	NR	34.4
DeFilippis 2006	IFX + MTX	22 weeks	16	1.67 (0.68)	NR	NR	20
DeFilippis 2006	ETN + MTX	54 weeks	16	1.89 (0.65)	5.07	NR	45.4
DeFilippis 2006	IFX + MTX	54 weeks	16	1.67 (0.68)	6.12	NR	13.7

[a] = $p<0.01$

Table 361: HAQ-DI Population 2/3 vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
AIM kremer 2006 Russell 2007	MTX+PBO	12months	219	1.7(0.6)	(estimate from graph 1.3)	adjusted -0.50(0.05)	NR
AIM Russell 2007	ABTi.v.+ MTX	12months	433	1.7(0.7)	(estimate from graph 1.05)	adjusted -0.68(0.03)	NR
ASSURE	PBO + cDMARDs	1 year (primary endpoint and study RCT endpoint)	413	1.5 (0.7) (n=418)	NR	-0.26	9
ASSURE	ABT + cDMARDs	1 year (primary endpoint and study RCT endpoint)	845	1.5 (0.6) (n=856)	NR	-0.47	30
CHANGE	PBO	24weeks	87	1.4 (0.7)	NR	0.1 (0.6)	NR
CHANGE	ADAmon	24weeks	91	1.6 (0.7)	NR	-0.2 (0.6)	NR
DE019	MTX+PBO n=200	52weeks	200	1.48 (0.59)	NR	-0.25(0.56)	-16.9
DE019	ADA+MTX n=207	52weeks	207	1.45 (0.63)	NR	-0.59(0.57)	-40.7
van de Putte 2004	PBO s.c.	26 weeks	110	1.88 (0.64)	NR	- 0.07 (0.49)	+ 1.8
van de Putte 2004	ADA mon	26 weeks	113	1.83 (0.59)	NR	- 0.38 (0.60)	- 21.3 [b]
ARMADA	MTX+PBO	24weeks	62	1.64 (0.63)	NR	0.27	-16.5
ARMADA	ADA+MTX	24weeks	67	1.55 (0.61)	NR	0.57	-40.0 [b]
CERTAIN	PBO + cDMARDs	24 weeks (primary endpoint and study RCT endpoint)	98	1.11 (0.62)	NR	[redacted]	NR
CERTAIN	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + DMARDs	24 weeks (primary endpoint and study RCT endpoint)	96	1.04 (0.60)	NR	[redacted]	NR
REALISTIC	PBO + existing cDMARDs	12 weeks	29	NR	NR	-0.10 [d]	NR
REALISTIC	CTZ 400mg weeks 0, 2, 4 then 200mg every 2 weeks + existing cDMARDs	12 weeks	134	NR	NR	-0.48 [d]	NR
ADORE	ETNmon n=159	16 weeks	142	1.6	NR	-0.59 (0.69)	NR
ADORE	ETN+MTX n=155	16 weeks	141	1.7	NR	-0.59 (0.58)	NR
ETN Study 309 (Combe 2006)	SSZ+PBO n=50	24weeks	50	1.6(0.5)	1.5(NR)	NR	9.2
ETN Study 309	ETN+PBO	24weeks	103	1.7(0.6)	1.1(NR)	NR	35.3 [b] vs SSZ

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
(Combe 2006)	n=103						
ETN Study 309 (Combe 2006)	ETN+SSZ n=101	24weeks	101	1.6(0.6)	1.0(NR) [a] vs SSZ non-sig vs ETN+PBO	NR	40.2 [b] vs SSZ non-sig vs ETN+PBO
ETN Study 309 (Combe 2006) Combe 2009	SSZ+PBO n=50	104weeks	50	NR	(estimate from graph 1.6)	NR	NR
ETN Study 309 (Combe 2006)	ETN+PBO n=103	104weeks	103	NR	(estimate from graph 1.1) [b] vs SSZ	NR	NR
ETN Study 309 (Combe 2006)	ETN+SSZ n=101	104weeks	101	NR	(estimate from graph 0.9) [b] vs SSZ	NR	NR
JESMR	ETN 25mg Q2W monotherapy	24 weeks (primary endpoint)	69	1.3 (0.8)	0.9 (0.8)	NR	NR
JESMR	ETN 25mg Q2W + MTX 6-8mg/week	24 weeks (primary endpoint)	73	1.2 (0.7)	0.7 (0.6)	NR	NR
JESMR	ETN 25mg Q2W monotherapy	52 weeks (primary endpoint)	69	1.3 (0.8)	0.9 (0.7)	NR	NR
JESMR	ETN 25mg Q2W + MTX 6-8mg/week	52 weeks (primary endpoint)	73	1.2 (0.7)	0.6 (0.6)	NR	NR
Lan 2004	PBO+MTX Placebo plus MTX	12 weeks (primary endpoint and study RCT endpoint)	29	1.23	0.99	-0.24	NR
Lan 2004	ETN+MTX Etanercept 25mg twice weekly plus MTX	12 weeks (primary endpoint and study RCT endpoint)	29	0.99	0.34	-0.65	NR
LARA	MTX+DMARD	24weeks	142	1.6(0.7)	NR	adjusted (SE) -0.9(0.1)	NR
LARA	ETN50+MTX	24weeks	279	1.6(0.7)	NR	adjusted (SE) -0.5adjusted between groups [b]	NR
Moreland 1999	PBO	6months	80	1.66(0.06)	NR	-0.12	NR
Moreland 1999	ETN+PBO	6months	78	1.63(0.06)	NR	-0.59 [a]	NR
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178	24weeks	155	(HAQ 0-3) 1.4(0.8)	0.97(0.85)	-0.44(0.77)	NR
RACAT (O'Dell 2013)	ETN50+MTX n=175	24weeks	160	1.5(0.8)	0.98(0.87)	-0.51(0.84)	NR
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178 randomised	48 weeks	155	NR	0.93 (0.85)	-0.46(0.82)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
	In analysis n=155 (of whom 39 switched to ETN)						
RACAT (O'Dell 2013)	ETN50+MTX n=175 randomised In analysis n=155 (of whom 41 switched to MTX+SSZ+HCQ)	48 weeks	155	NR	0.83 (0.81)	-0.64(0.78)	NR
Wajdula 2000	PBO	12weeks	81	1.8	NR	1.70 (0.60)	NR
Wajdula 2000	ETN	12weeks	99	1.9	NR	1.30 (0.60)	NR
Weinblatt 1999	MTX plus placebo	24weeks	30	1.5 [c]	1.1 [c]	NR	NR
Weinblatt 1999	ETN + MTX	24weeks	59	1.5 [c]	0.8 [c] [b]	NR	NR
APPEAL	MTX plus DMARD (SSZ, HCQ or leflunomide)	16 weeks (primary endpoint and study RCT endpoint)	103	1.4 (0.7)	0.9	NR	38.3
APPEAL	Etanercept 25mg twice weekly (licensed dose) plus MTX	16 weeks (primary endpoint and study RCT endpoint)	197	1.4 (0.7)	0.7	NR	49.4
GO-FORTH	PBO Q4W + MTX 6-8mg/week	14 weeks (primary endpoint)	88	1.0 (0.68)	NR	0.07 (0.49)	NR
GO-FORTH	GOL 50mg s.c. Q4W + MTX 6-8mg/week	14 weeks (primary endpoint)	86	1.0 (0.61)	NR	0.32 (0.40)	NR
GO-FORTH	PBO Q4W + MTX 6-8mg/week	24 weeks (study RCT endpoint)	88	1.0 (0.68)	NR	0.03 (0.58)	NR
GO-FORTH	GOL 50mg s.c. Q4W + MTX 6-8mg/week	24 weeks (study RCT endpoint)	86	1.0 (0.61)	NR	0.33 (0.42)	NR
GO-FORWARD [359]	PBO s.c. every 4 weeks + MTX	14 weeks	133	Mean 1.3 (0.7) 1.250 (0.750 to 1.750) [c]	NR	Mean change – 0.16 (0.49) - 0.13 (- 0.38 to 0.13) [c]	NR
GO-FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	14 weeks	89	Mean 1.4 (0.7) 1.375 (1.000 to 1.875) [c]	NR	Mean change 0.42 (0.50) (P<0.001 vs. PBO) - 0.38 (- 0.75 to – 0.13) [c] ([b] vs PBO + MTX)	NR
GO-FORWARD	PBO s.c. every 4 weeks + MTX	24 weeks	133	Mean 1.3 (0.7) (0.750 to 1.750) [c]	NR	Mean change - 0.13 (0.58) - 0.13 (- 0.38 to 0.13) [c]	NR
GO-FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	24 weeks	89	Mean 1.4 (0.7)	NR	Mean change 0.47 (0.55) (P<0.001 vs. PBO)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
				(1.000 to 1.875) [c]		- 0.38 (- 0.75 to – 0.13) [c] ([b] vs PBO + MTX)	
ATTRACT	PBO i.v. + MTX	30 weeks	88	HAQ (0-3) = 1.8 (1.3, 2.1) [c]	HAQ (0-3) = 1.5 (1.0, 2.0) [c]	NR	- 3
ATTRACT	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter	30 weeks	86	HAQ (0-3) = 1.8 (1.4, 2.3) [c]	HAQ (0-3) = 1.5 (0.9, 2.1) [c]	NR	- 13 (P=0.167)
ATTRACT [179]	PBO i.v. + MTX	54 week	68	1.8 (1.3, 2.1) [c]	NR	HAQ change = 0 [c] (range 0.0 – 2.2)	% achieving HAQ change ≥ 0.25 = 43
ATTRACT	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter	54 week	77	HAQ (IQR) = 1.8 (1.4, 2.3) [c]	NR	HAQ improvement 0.4 [c] (range 0.0 – 1.9)	% achieving HAQ change ≥ 0.25 = 69 [b]
Durez 2004	Single i.v. infusion of 1 g MP at week 0 + MTX (15 randomised)	14 weeks	NR	HAQ (range) = 1.5 [c] (0.75-2.13)	Mean = 1.55	NR	NR
Durez 2004	IFX 3 mg/kg at weeks 0, 2 and 6 + MTX (12 randomised)	14 weeks	NR	HAQ (range) = 1.3 [c] (0.75-2)	Mean = 0.95 [a]	NR	NR
START	PBO + MTX	22 weeks (primary endpoint and study RCT endpoint)	363	1.5 (1-2) [c]	NR	-0.11	NR
START	IFX 3mg/kg + MTX	22 weeks (primary endpoint and study RCT endpoint)	360	1.5 (1-2) [c]	NR	-0.39	NR
Zhang 2006	PBO i.v. + MTX (86 randomised, 71 completed)	18 weeks	NR	NR	NR	HAQ score decreased by 0.45 (unclear whether mean value reported)	NR
Zhang 2006	IFX 3 mg/kg i.v. at weeks 0, 2, 6 and 14 + MTX (87 randomised, 78 completed)	18 weeks	NR	NR	NR	HAQ score decreased by 0.76 (unclear whether mean value reported) [b]	NR
ACT-RAY	TCZ 8 mg/kg i.v. every 4 weeks + oral PBO	24 weeks	276	1.48 (0.60)	NR	- 0.54	NR
ACT-RAY	TCZ 8 mg/kg i.v. every 4 weeks + MTX	24 weeks	277	1.46 (0.66)	NR	- 0.56	NR
SATORI	PBO i.v. every 4 weeks + MTX	24 weeks	64	MHAQ 0.76	MHAQ 0.62	NR	NR
SATORI	TCZ 8 mg/kg i.v. every 4 weeks+ PBO capsules	24 weeks	61	MHAQ 0.79	MHAQ 0.43	NR	NR
TOWARD	PBO i.v. every 4 weeks + stable cDMARDs (415	24 weeks	413	1.5 (0.6)	NR	- 0.2	% achieving ≥ 0.3 change from

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean HAQ-DI score at baseline (0-3) (SD)	Mean HAQ-DI score at follow-up (0-3) (SD)	HAQ-DI mean change from baseline (SD)	% change from baseline
	randomised)						baseline = 34
TOWARD	TCZ 8 mg/kg i.v. every 4 weeks + stable DMARDs (805 randomised)	24 weeks	803	1.5 (0.6)	NR	- 0.5 [b]	% achieving ≥ 0.3 change from baseline = 60
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR

[a] = p<0.05
[b] = p<0.01
[c] = median (IQR)

Table 362: Joint counts and assessment of inflammation markers: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
HIT HARD	MTX + PBO	24 weeks	10.7 (4.5) (0-28 scale)	3.6 (4.9) (0-28 scale)	NR	13.1 (5.9) (0-28 scale)	5.0 (6) (0-28 scale)	NR	17 (7-34) [c] mg/l	7.1 (8.1)	36 (29-55) [c]	18.7 (14.2)
	ADA + MTX	24 weeks	10.2 (5.0) (0-28 scale)	1.4 (2.2) [b] (0-28 scale)	NR	13.0 (6.5) (0-28 scale)	3.2 (4.8) [a] (0-28 scale)	NR	12 (6-37) [c] mg/l	5.7 (10.3)	33 (29-45) [c]	16.1 (13.3)
OPERA	MTX + PBO + steroid	12 months	Median (5th, 95th centile range): 11 (3-31)	Median (5th, 95th centile range): 0 (0-3)	NR	Median (5th, 95th centile range): 16 (6-34)	Median (5th, 95th centile range): 0 (0-9)	NR	15 (7-109) [d]	7 (7-44) [d]	NR	NR
	ADA + MTX + steroid	12 months	Median (5th, 95th centile range): 10 (3-33)	Median (5th, 95th centile range): 0 (0-6)	NR	Median (5th, 95th centile range): 15 (5-38)	Median (5th, 95th centile range): 0 (0-13)	NR	15 (7-133) [d]	7 (7-21) [d]	NR	NR
OPTIMA	MTX + PBO	26 weeks	12 (5.8) (0-28 scale) 18 (11) (0-66 scale)	5.8 (0-28 scale)	NR	16 (6.7) (0-28 scale) 27 (15) (0-68 scale)	7.6 (0-28 scale)	NR	30 (33) mg/l	11.7	NR	NR
	ADA + MTX	26 weeks	13 (5.8) (0-28 scale) 18 (11) (0-66 scale)	3.6 (0-28 scale)	NR	16 (6.6) (0-28 scale) 29 (15) (0-68)	5.3 [a] (0-28 scale)	NR	27 (32) mg/l	7.1 [a]	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
PREMIER [360]	MTX + PBO	1 year	22.1 (11.7) (0-66 scale)	NR	NR	32.3 (14.3) (0-68 scale)	NR	NR	4.0 (4.0)	NR	NR	NR
	ADA monotherapy + PBO step up week 16	1 year	21.8 (10.5) (0-66 scale)	NR	NR	31.8 (13.6) (0-68 scale)	NR	NR	4.1 (3.9)	NR	NR	NR
	ADA + MTX step up week 16	1 year	21.1 (11.2) (0-66 scale)	NR	NR	30.7 (14.2) (0-68 scale)	NR	NR	3.9 (4.2)	NR	NR	NR
PREMIER [360]	MTX + PBO	2 years	22.1 (11.7) (0-66 scale)	NR	NR	32.3 (14.3) (0-68 scale)	NR	NR	4.0 (4.0)	NR	NR	NR
	ADA monotherapy + PBO step up week 16	2 years	21.8 (10.5) (0-66 scale)	NR	NR	31.8 (13.6) (0-68 scale)	NR	NR	4.1 (3.9)	NR	NR	NR
	ADA + MTX step up week 16	2 years	21.1 (11.2) (0-66 scale)	NR	NR	30.7 (14.2) (0-68 scale)	NR	NR	3.9 (4.2)	NR	NR	NR
COMET [135]	MTX +PBO n=268	52 weeks	mean DAS28 swollen-joint count 12.3	4.3	65 % improvement	NR	NR	NR	NR	NR	NR	NR
	ETN+MTX n=274		12.4	1.8	85 % improvement [a]	NR	NR	NR	NR	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
COMET [135]	MTX in year 1 MTX in year 2 n=99 at start of period 2	From week 52 to week 104	2.4	2.9	NR	NR	NR	NR	NR	NR	NR	NR
	MTX year 1 ETN+MTX in year 2 n=90 at start of period 2		2.6	1.3 [b] vs. MTX/MTX	NR	NR	NR	NR	NR	NR	NR	NR
COMET	ETN+MTX in year 1 ETN+MTX in year 2 n=111 at start of period 2		1.7	1.3	NR	NR	NR	NR	NR	NR	NR	NR
	ETN+MTX in year 1 ETN in year 2 n=111 at start of period 2		1.1	1.7	NR	NR	NR	NR	NR	NR	NR	NR
ERA [361]	MTX + PBO	6 months	24 (11.9)	NR	NR	30 (16.1)	NR	NR	3.7	NR	NR	NR
	ETN 25mg Q2W + PBO	6 months	24 (11.9)	NR	NR	31 (15.8)	NR	NR	3.3	NR	NR	NR
ERA [361]	MTX + PBO	12 months	24 (11.9)	NR	NR	30 (16.1)	NR	NR	NR	NR	NR	NR
	ETN 25mg Q2W + PBO	12 months	24 (11.9)	NR	NR	31 (15.8)	NR	NR	NR	NR	NR	NR
GO-BEFORE	PBO + MTX	24 weeks	(0-66) 14.9 (10.01)	NR	66.7 [c]	(0-68) 27.3 (16.16)	NR	57.1 [c]	2.6 (3.28)	NR	NR	NR
	GOL 50 mg s.c.	24 weeks	16.0	NR	75.6 [c]	29.2	NR	67.2 [a,c]	2.4 (3.02)	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	every 4 weeks + MTX		(9.98)			(17.05)						
Durez 2007	MTX	52 weeks (study RCT endpoint)	10.3 (5.5)	NR	NR	11.6 (7.5)	NR	NR	2.5 (3.5) [7 (3-121) [c] mg/l]	2.5 (1-31) [c] mg/l	NR	NR
	MTX + i.v. methylprednisolone (MP)	52 weeks (study RCT endpoint)	12.4 (7.6)	NR	NR	13.2 (9.1)	NR	NR	4.7 (5.1) [32 (3-213)[c] mg/l]	7.5 (1-27) [c] mg/l	NR	NR
	IFX 3 mg/kg i.v. at weeks 0, 2, 6, 14, 22, 30, 46	52 weeks (study RCT endpoint)	12.5 (5.4)	NR	NR	15.9 (8.0)	NR	NR	4.8 (5.2) [19 (1-29)[c] mg/l]	3.5 (1-29) [c] mg/l	NR	NR
Quinn 2005	MTX + PBO	14 weeks	NR	NR	NR	NR	NR	NR	37 (38.8) mg/l	41 [e]	NR	NR
	IFX 3mg/kg + MTX	14 weeks	NR	NR	NR	NR	NR	NR	47 (27.9) mg/l	7 [e]	NR	NR
Quinn 2005	MTX + PBO	54 weeks	NR	NR	NR	NR	NR	NR	37 (38.8) mg/l	10 [e]	NR	NR
	IFX 3mg/kg + MTX	54 weeks	NR	NR	NR	NR	NR	NR	47 (27.9) mg/l	8 [e]	NR	NR

a = P<0.05
b = P<0.001
c =Median (IQR)
d = Median (5th, 95th centile range)
e = Estimated from graphical data
f = Mean % change
g = Median % change
h = Adjusted mean change (SE)
i = Mean change (SD)
j = Median (range)

Table 363: Joint counts and assessment of inflammation markers: Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
AMPLE	ABT s.c. + MTX	1 year	15.8 (9.8) (0-66 scale)	NR	70.9 improved	25.4 (15.3) (0-68 scale)	NR	59.8 improved	1.6 (2.1)	0.80 (1.13)	NR	NR
	ADA + MTX	1 year	15.9 (10.0) (0-66 scale)	NR	68.2 improved	26.3 (15.8) (0-68 scale)	NR	61.4 improved	1.5 (2.8)	0.65 (1.21)	NR	NR
REDSEA	ADA+cDMARDs(REDSEA) n=60	12months	(scale 0-28) 9 (5–12) [c]	4 (1–6) [c]		(scale 0-28) 14 (9–20) [c]	5 (1–14) [c]		10 (5–22) [c]	6 (3–14) [c]		
	ETN50+cDMARDs(REDSEA) n=60		(scale 0-28) 9 (6–13) [c]	5 (2–11) [c]		(scale 0-28) 14 (8–20) [c]	8 (4–14) [c]		12.5 (5–31) [c]	9 (3–14) [c]		
De Filippis 2011	ETN + MTX	54 weeks	16.87 (7.31)	Conflicting data	49.5	22.40 (8.10)	Conflicting data	-61.3 [a]	NR	NR	35.47 (20.31)	Conflicting data
	IFX + MTX	54 weeks	14.73 (5.04)	Conflicting data	45.3	20.93 (9.97)	Conflicting data	-24.33	NR	NR	38 (26.28)	Conflicting data
ADACTA	TCZ 8 mg/kg i.v. every 4 weeks + s.c. PBO ADA	24 weeks	(0-28 scale) 11.3 (5.3)	(0-66 scale) 6.7 (10.7)	NR	(0-28 scale) 15.9 (6.7)	(0-68 scale) 12.7 values	NR	NA	NR	NA	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
							NR)					
	ADA 40 mg s.c. every 2 weeks + i.v. PBO TCZ	24 weeks	12.4 (5.4)	8.6 (10.5)	NR	16.5 (7.0)	16.8 (16.2)	NR	NA	NR	NA	NR

a = P<0.05
b = P<0.001
c =Median (IQR)
d = Median (5th, 95th centile range)
e = Estimated from graphical data
f = Mean % change
g = Median % change
h = Adjusted mean change (SE)
i = Mean change (SD)
j = Median (range)

Table 364: Joint counts and assessment of inflammation markers: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
AIM [59]	MTX+PBO n=219	12 months	(scale unclear) 22.1 (8.8)	NR	adjusted mean change - 11.5(0.54)	(scale unclear) 32.3 (13.6)	NR	adjusted mean change - 16.3(0.85)	28 (25)	adjusted mean change - 8.2(1.4)	NR	NR
	ABTi.v.+ MTX n=433		21.4 (8.8)	NR	adjusted mean change - 16.1(0.35)	31.0 (13.2)	NR	adjusted mean change - 22.5(0.55)	33 (31)	adjusted mean change - 18.3(0.9)	NR	NR
ASSET	PBO + MTX	4 months	8.5 (4.1) (scale NR)	NR	NR	13.3 (7.2) (scale NR)	NR	NR	16.6 (16.	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
									8) mg/l			
	ABT i.v. (~10mg/kg) + MTX	4 months	11.3 (6.6) (scale NR)	NR	NR	12.9 (7.1) (scale NR)	NR	NR	13.6 (17.4) mg/l	NR	NR	NR
CHANGE	PBO n=87	24weeks	[scale unclear] 19.3(7)	NR	mean change - 1.8(7.4)	[scale unclear] 23.7(8.8)	NR	mean change - 0.5(10.9)	5.9(3.3)	mean change 0.1(3.2)	NR	NR
	ADAmon n=91		19.1(7.3)	NR	mean change - 8.2(8.8) [a]	24.4(10.7)	NR	mean change -10.7 (12.3) [a]	6.5(4.4)	mean change -1.6 (4.1) [a]	NR	NR
ADORE van	ETNmon n=159 n=156 at 16	16 weeks		NR	NR	NR	NR	NR	NR	NR	33.2	26.4

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
Riel 2006	weeks											
	ETN+MTX n=155 n=151 at 16weeks			NR	NR	NR	NR	NR	NR	NR	36.7	20.8 [b]
ETN 309	SSZ+PBO n=50	24weeks	[scale unclear]	NR	38.5 Improvement	painful joints [scale unclear]	NR	painful joints 22.7 improvement	NR	32.9 [g]	NR	0.2 [f]
	ETN+PBO n=103			NR	68.7 Improvement		NR	65.4 Improvement	NR	69.9 [a] (vs. SSZ), [g]	NR	37.6 [a (vs. SSZ), f]
	ETN+SSZ n=101			NR	70.1 [a] vs. SSZ improvement		NR	62.0 improvement	NR	66.7 [a] (vs. SSZ), [g]	NR	43.0 [a (vs. SSZ), f]
JESMR	ETN 25mg Q2W	24 weeks	12.4 (6.1) (0-66 scale)	4.3 (5.2)	NR	15.0 (9.4) (0-68 scale)	4.5 (8.0)	NR	2.5 (2.5	1.2 (1.7	59.7 (28.4)	41.6 (25.4)

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	monotherapy								)	)		
	ETN 25mg Q2W + MTX 6-8mg/week	24 weeks	12.5 (6.5) (0-66 scale)	3.0 (3.8)	NR	15.1 (8.1) (0-68 scale)	2.4 (3.9)	NR	3.0 (3.2)	0.6 (1.0) [a]	59.5 (26.5)	29.9 (23.3) [a]
JESMR	ETN 25mg Q2W monotherapy	52 weeks	12.4 (6.1) (0-66 scale)	4.0 (4.4)	NR	15.0 (9.4) (0-68 scale)	4.3 (5.3)	NR	2.5 (2.5)	1.3 (1.6)	59.7 (28.4)	43.7 (27.0)
	ETN 25mg Q2W + MTX 6-8mg/week	52 weeks	12.5 (6.5) (0-66 scale)	1.8 (2.3) [a]	NR	15.1 (8.1) (0-68 scale)	2.1 (2.8) [a]	NR	3.0 (3.2)	3.0 (3.2) [b]	59.5 (26.5)	28.9 (23.8) [b]
Lan 2004	PBO+MTX Placebo plus MTX	12 weeks	14.45 (0-28 scale)	10.59 (0-28 scale)	27	16.00 (0-28 scale)	13.55 (0-28 scale)	15	1.83	1.38	NR	NR
	ETN+MTX Etanercept 25mg twice weekly plus MTX	12 weeks	13.21 (0-28 scale)	4.66 [a] (0-28 scale)	65	14.03 (0-28 scale)	7.03 [a] (0-28 scale)	50	1.65	0.39 [a]	NR	NR
LARA	MTX+DMARD(LAR	24weeks	(scale unclear)	NR	–8.6 (0.6)	(scale unclear)	NR	–12.8 (0.8)	NR	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	A) n=142		19.3 (10.1)		[h]	26.2 (12.3)		[h]				
	ETN50+MTX n=281(n=279 at week24)		18.2 (8.4)	NR	–15.1 (0.4) [a,h]	25.1 (11.9)	NR	–19.8 (0.6) [a,h]	NR	NR	NR	NR
Moreland 1999 Mathias 2000 data from Moreland 1999	PBO n=80	6months	(scale 0-68) 25	NR	7% (worsening)	(scale 0-71) 35	NR	-6%	4.1	207% worse [f]	39	18% worse [f]
	ETN+PBO n=78		25	NR	-47 [b]	33	NR	-56% [a]	4.7	31% improved [b,f]	35	18% improved [a,f]
RACAT	MTX+SSZ+HCQ n=178 (not all analysed)	24weeks	(scale 0-28) 11.12 (5.26)	5.32 (4.73)	NR	(scale 0-28) 13.39 (6.62)	5.87 (5.96)	NR	NR	NR	27.39 (21.03)	20.38 (16.73) change 0.97(0.85)

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	ETN50+MTX n=175(not all analysed)		(scale 0-28) 11.34 (5.22)	4.76 (5.14)	NR	(scale 0-28) 13.39 (6.39)	5.94 (6.85)	NR	NR	NR	29.80 (23.51)	19.01 (17.89) change 0.98(0.87)
RACAT	MTX+SSZ+HCQ n=178 (not all analysed) some switched	48weeks n=310 both groups	NR	NR	3.93 (4.19)	NR	4.64 (5.61)	NR	NR	NR	NR	18.88 (15.35)
	ETN50+MTX n=175(not all analysed) some switched		NR	NR	3.50 (3.87)	NR	4.61 (6.10)	NR	NR	NR	NR	19.76 (18.30)
Weinblatt 1999	MTX plus placebo, n=30	24weeks	(scale 0-68) 17 [c]	16 [c]	NR	(scale 0-71) 28 [c]	17 [c]	NR	2.6 [c]	1.6 [c]	36 [c]	30 [c]
	Etanercept 25mg twice		20 [c]	6 [b,c]	NR	28 [c]	7 [b,c]	NR	2.2 [c]	0.5 [b,c]	25 [c]	15 [a,c]

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	weekly plus MTX, n=59											
APPEAL	MTX plus DMARD (SSZ, HCQ or leflunomide)	16 weeks	NR	NR	NR	NR	NR	NR	2.06 (2.48) calculated from 20.6 (24.8) mg/L	9.8 (52.2)	54.80 (28.2)	40.4 (26.2)
	Etanercept 25mg twice weekly (licensed dose) plus MTX	16 weeks	NR	NR	NR	NR	NR	NR	1.70 (2.10) calculated from 17.0	7.9 (53.3)	57.7 (33.0)	34.4 (40.4) [a]

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
									(21.0) mg/L			
GO-FORTH	PBO Q4W + MTX 6-8mg/week	14 weeks	11.4 (6.58) (0-66 scale)	NR	NR	13.2 (7.83) (0-68 scale)	NR	NR	NR	NR	NR	NR
	GOL 50mg s.c. Q4W + MTX 6-8mg/week	14 weeks	11.8 (6.72) (0-66 scale)	NR	NR	13.1 (8.38) (0-68 scale)	NR	NR	NR	NR	NR	NR
GO-FORTH	PBO Q4W + MTX 6-8mg/week	24 weeks	11.4 (6.58) (0-66 scale)	NR	NR	13.2 (7.83) (0-68 scale)	NR	NR	NR	NR	NR	NR
	GOL 50mg s.c. Q4W + MTX 6-8mg/week	24 weeks	11.8 (6.72) (0-66 scale)	NR	NR	13.1 (8.38) (0-68 scale)	NR	NR	NR	NR	NR	NR
GO-FORWARD	PBO s.c. every 4 weeks + MTX	Week 14	12.0 (8.0 to 19.0) [c] (0-66 scale)	NR	37.5 (0.0, 71.4) [c] As report	21.0 (14.0 to 34.0) [c] (0-68 scale)	NR	30.0 (-12.1, 66.7) [c] As	0.80 (0.30 to 2.00) [c]	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
					ed			reported				
	GOL 50 mg s.c. every 4 weeks + MTX	Week 14	13.0 (8.0 to 22.0) [c] (0-66 scale)	NR	62.1 (28.6, 84.6) [b,c] As reported	26.0 (16.0 to 39.0) [c] (0-68 scale)	NR	59.5 (24.0, 77.8) [a,c] As reported	1.00 (0.40 to 2.80) [c]	NR	NR	NR
GO-FORWARD	PBO s.c. every 4 weeks + MTX	Week 24	12.0 (8.0 to 19.0) [c]	NR	32.1 (-9.1, 71.4) [c] As reported	21.0 (14.0 to 34.0) [c] As reported	NR	20.9 (-13.3, 64.3) [c]	NR	NR	NR	NR
	GOL 50 mg s.c. every 4 weeks + MTX	Week 24	13.0 (8.0 to 22.0) [c]	NR	72.1 (24.0, 92.3) [b,c] As reported	26.0 (16.0 to 39.0) [c] As reported	NR	61.6 (18.7, 85.4) [c]	NR	NR	NR	NR
ATT	PBO i.v. +	30 weeks	(0-66)	13 (8, 26) [c]	- 20	(0-68)	16 (7, 33) [c]	- 26	3.0	2.3	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
RACT	MTX		19 (13, 28) [c]			24 (16, 48) [c]			(1.2, 5.7) [c]	(0.7, 5.1) [c] (-9% change)		
	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter	30 weeks	(0-66) 19 (13, 30) [c]	9 (4, 18) [b,c]	- 52 [b]	(0-68) 32 (16, 46) [c]	12 (3, 21) [a,c]	- 59 [a]	3.1 (1.3, 5.3) [c]	0.8 (0.4, 2.3) [b,c] (-60 % change) [b]	NR	NR
ATTRACT [139]	PBO i.v. + MTX	54 week	(0-66) 19 (13, 28) [c]	NR	13 (61) [i] As reported	(0-68) 24 (16, 48) [c]	NR	23 (63) [i] As reported	NA	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter	54 week	(0-66) 19 (13, 30) [c]	NR	37 (62) [b,i] As reported	(0-68) 32 (16, 46) [c]	NR	49 (52) [b,i] As reported	NA	NR	NR	NR
Durez 2004	Single i.v. infusion of 1 g MP at week 0 + MTX (15 randomised)	14 weeks	22 (7-38) [j] (0-66 scale)	22	NR	24 (7-38) [j] (0-68 scale)	20	NR	1.9 [j]	2.0	NR	NR
	IFX 3 mg/kg at weeks 0, 2 and 6 + MTX (12 randomised)	14 weeks	16 (8-27) [j] (0-66 scale)	7 [b]	NR	20 (6-44) [j] (0-68 scale)	8 [a]	NR	1.3 [j]	0.9	NR	NR
START	PBO + MTX	22 weeks	15 (10-21) [c] (0-66 scale)	NR	NR	22 (15-32) [c] (0-68 scale)	NR	NR	1.2 (1-	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
									3) [c]			
	IFX 3mg/kg + MTX	22 weeks	15 (11-21) [c] (0-66 scale)	NR	NR	22 (15-31) [c] (0-68 scale)	NR	NR	1.6 (1-3) [c]	NR	NR	NR
Wong 2009	PBO + MTX (with crossover for PBO group to open-label IFX at week 24).	Week 16	(0-28 scale) 12 (5)	12	NR	(0-28 scale) 15 (7)	16	NR	3.0	22	40 (24)	37
	IFX 3 mg/kg at weeks 0, 2, 6 and 8 weeks thereafter + MTX	Week 16	10 (5)	4	NR	14 (7)	8 [a]	NR	3.2	12	39 (26)	26
ACT-RAY	TCZ 8 mg/kg i.v. every 4 weeks + oral PBO	Week 24	15.3 (10.2) (scale NR)	NR	-11.75 (9.45) [i]	26.6 (15.2) (scale NR)	NR	-17.00 (13.64) [i]	NR	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	TCZ 8 mg/kg i.v. every 4 weeks + MTX	Week24	14.4 (8.9) (scale NR)	NR	-11.33 (8.04) [i]	25.8 (13.9) (scale NR)	NR	-17.25 (13.35) [i]	NR	NR	NR	NR
SATORI [362]	PBO i.v. every 4 weeks + MTX	24 weeks	(0-28) 12 [e]	(0-28) 9 [e]	NR	(0-28) 10.5 [e]	(0-28) 7 [e]	NR	2.6 [e]	7 [e]	50 [e]	45 [e]
	TCZ 8 mg/kg i.v. every 4 weeks+ PBO capsules	24 weeks	(0-28) 10 [e]	(0-28) 4.5 [e]	NR	(0-28) 10 [e]	(0-28) 2 [e]	NR	3.0 [e]	2 [e]	50 [e]	11 [e]
TOWARD	1) PBO i.v. every 4 weeks + stable cDMARDs (415 randomised)	24 weeks	(0-68) 18.7 (10.8)	13.8	NR	(0-66) 29.1 (14.8)	20.6	NR	2.6 (4.7)	2.33	49.2 (28.3)	44.5
	2) TCZ 8	24 weeks	19.7 (11.6)	9.4 [b]	NR	30.1 (16.0)	14.4 [b]	NR	2.6	0.4	48.2	12.6 [b]

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Mean swollen joint count at baseline (SD) (scale)	Mean swollen joint count at follow-up (SD) (scale)	Swollen joint count % change from baseline	Mean tender joint count at baseline (SD) (scale)	Mean tender joint count at follow-up (SD) (scale)	Tender joint count % change from baseline	CRP level at baseline (mean) (mg/dl)	CRP level at follow-up (mean) (mg/dl)	ESR level at baseline (mean) (mm/hr)	ESR level at follow-up (mean) (mm/hr)
	mg/kg i.v. every 4 weeks + stable DMARDs (805 randomised)								(3.2)	[b]	(27.5)	

a = P<0.05
b = P<0.001
c =Median (IQR)
d = Median (5th, 95th centile range)
e = Estimated from graphical data
f = Mean % change
g = Median % change
h = Adjusted mean change (SE)
i = Mean change (SD)
j = Median (range)

Table 365: Global assessments of disease activity: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
OPERA [97]	PBO + MTX + steroid	12 months	65 (17-96) [c]	18 (0-69) [c]	NR	51 (22-86) [c]	4 (0-33) [c]	NR
	ADA + MTX + steroid	12 months	70 (12-100) [c]	10 (0-54) [c]	NR	57 (22-86) [c]	1 (0-59) [c]	NR
OPTIMA	PBO + MTX	26 weeks	63 (22)	35.1	NR	62 (18)	28.9	NR
	ADA + MTX	26 weeks	64 (23)	26.4	NR	63 (18)	21.3	NR
GO-BEFORE	PBO + MTX	24 weeks	(0-10 scale) 5.9 (2.32)	NR	- 36.70	(0-10 scale) 6.0 (1.72)	NR	- 63.00
	GOL + MTX	24 weeks	(0-10 scale) 6.1 (2.21)	NR	- 49.55 [a]	(0-10 scale) 6.2 (1.63)	NR	- 66.70
BeST [363]	Sequential monotherapy	6 months	59.2	NR	Mean change from BL= -22.3	NR	NR	NR
	Step-up combination therapy	6 months	59.4	NR	Mean change from BL= -28.0	NR	NR	NR
	Initial combination therapy + prednisone	6 months	59.5	NR	Mean change from BL= -32.0 [a for sequential mono vs. initial combo + pred and initial combo + MTX]	NR	NR	NR
	Initial combination	6 months	61.8	NR	Mean change from BL= -	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
	therapy + IFX				35.9 [a] for sequential mono vs. initial combo + pred and initial combo + MTX			

[a] = *P<0.05*
[b] = *P<0.001*
[c] =*Median (IQR)*
[d] = *Reported on 0-100 VAS scale unless otherwise stated*
[e] = *Estimated from graphical data*

Table 366: Global assessments of disease activity: Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
AMPLE	ABT s.c.	12 months	61.1 (22.1)	NR	46.1 (as reported)	58.8 (18.6)	NR	68.5 (as reported)
	ADA	12 months	61.5 (22.5)	NR	41.2 (as reported)	58.8 (18.9)	NR	63.0 (as reported)
REDSEA	ADA +cDMARDs	12 months	70 (50–82)	49 (20–65)	NR	NR	NR	NR
	ETN50+cDMARDs	12 months	70 (54–80)	50 (27–71)	NR	NR	NR	NR
De Filippis 2011	ETN + MTX	22 weeks	64.33 (18.89)	NR	34.8 (as reported)	58.33 (14.60)	NR	38.3 (as reported)
	IFX + MTX	22 weeks	69.33 (16.57)	NR	21.4 (as reported)	60.67 (12.0)	NR	35.6 (as reported)
De Filippis 2011	ETN + MTX	54 weeks	64.33 (18.89)	74.88	50.6 (as reported)	58.33 (14.60)	77.05	41.8 (as reported)
	IFX + MTX	54 weeks	69.33 (16.57)	86.91	22.2 (as reported)	60.67 (12.0)	83.31	43.6 (as reported)

[a] = *P<0.05*
[b] = *P<0.001*
[c] =*Median (IQR)*
[d] = *Reported on 0-100 VAS scale unless otherwise stated*
[e] = *Estimated from graphical data*

Table 367: Global assessments of disease activity: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
AIM [59]	PBO + MTX	12 months	62.8 (21.6)	NR	adjusted mean change - 24.2 (1.72)	67.4 (17.0)	NR	adjusted mean change - 34.3 (1.44)
	ABT i.v.+ MTX	12 months	62.7 (21.2)	NR	adjusted mean change - 35.8 (1.12)	68.0 (16.0)	NR	adjusted mean change - 49.1 (0.93)
ASSURE	PBO + cDMARDs	1 year	61.3 (20.1)	NR	20	58.3 (17.5)	NR	37
	ABT + cDMARDs	1 year	60.6 (19.7)	NR	41	57.8 (17.4)	NR	56
CHANGE	PBO	24 weeks	64.6 (22.9)	NR	mean change 2.6 (23.5)	74.1(15.6)	NR	mean change - 8.0 (21.8)
	ADA monotherapy	24 weeks	71.2(19.2)	NR	mean change -19.9	76.2(14.7)	NR	mean change - 30.3

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
					(31.0) [a]			(24.8) [a]
DE019	PBO + MTX	52 weeks	54.3(22.9)	NR	- 20.1	61.3(17.3)	NR	- 31.8
	ADA + MTX	52 weeks	52.7(21.0)	NR	- 52.2	62.0(16.7)	NR	- 63.5
van de Putte 2004	PBO	26 weeks	71.8 (19.9)	NR	- 7.9	68.5 (18.2)	NR	- 12.9
	ADA monotherapy	26 weeks	72.6 (19.3)	NR	- 38.9 [b]	67.3 (16.6)	NR	- 38.8 [b]
ARMADA	PBO + MTX	24 weeks	58.0 (23.2)	NR	-14.7	58.9 (15.3)	NR	- 11.6
	ADA + MTX	24 weeks	56.9 (21.1)	NR	- 52.4 [b]	58.7 (15.8)	NR	- 53.0 [b]
Kim 2007	PBO + MTX	24 weeks	63.2 (20.44)	NR	mean change - 10.7 (24.85)	64.0 (13.61)	NR	mean change -9.6 (26.47)
	ADA+MTX	24 weeks	59.7 (17.19)	NR	mean change - 23.7 (26.54) [a]	63.7 (15.16)	NR	mean change -29.2 (27.48) [b]
ADORE	ETN monotherapy	16 weeks	(0-10 scale)	NR	(0-10	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
[56]			6.6		scale) mean change from baseline -2.78 (2.60)			
	ETN + MTX	16 weeks	(0-10 scale) 6.6	NR	(0-10 scale) mean change from baseline -2.95 (2.59)	NR	NR	NR
ETN309	PBO + SSZ	24 weeks	NR	NR	(0-10 scale) 13.6	NR	NR	(0-10 scale) 16.0
	ETN + PBO	24 weeks	NR	NR	50.5 [b vs. SSZ]	NR	NR	59.5 [b vs. SSZ]

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
	ETN + SSZ	24 weeks	NR	NR	53.5 [b vs. SSZ, NS vs. ETN + PBO]	NR	NR	62.0 [b vs. SSZ, NS vs. ETN + PBO]
JESMR	ETN monotherapy	24 weeks	62.5 (20.5)	31.5 (28.4)	NR	58.2 (21.5)	NR	NR
	ETN + MTX	24 weeks	53.7 (23.7)	21.6 (18.8)	NR	58.2 (19.3)	NR	NR
JESMR	ETN monotherapy	52 weeks	62.5 (20.5)	27.4 (25.1)	NR	NR	NR	NR
	ETN + MTX	52 weeks	53.7 (23.7)	21.3 (19.4)	NR	NR	NR	NR
Lan 2004	PBO+MTX	12 weeks	69.7	61.4	NR	79.7	54.2	NR
	ETN + MTX	12 weeks	66.2	37.9	NR	75.2	22.8	NR
LARA	MTX + DMARD	24 weeks	(1-10 scale) 7.1 (1.9)	NR	(1-10 scale) adjusted mean change (SE) –2.3 (0.2)	(1-10 scale) 6.7 (1.6)	NR	(1-10 scale) adjusted mean change (SE) –2.4 (0.2)
	ETN50 + MTX	24 weeks	(1-10 scale) 7.1 (2.0)	NR	(1-10 scale)	(scale 1-10)	NR	(1-10 scale)

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
					adjusted mean change (SE) –3.9 (0.2) [b]	6.7 (1.6)		adjusted mean change (SE) –4.8 (0.1) [b]
Moreland 1999 [94 95]	PBO	6 months	(0-10 scale) 6.9	NR	3 (worse)	(0-10 scale) 6.9	NR	2 (improved)
	ETN + PBO	6 months	(0-10 scale) 7.0	NR	6 (improved) between groups [b]	(0-10 scale) 6.9	NR	44 (improved) between groups [b]
RACAT	MTX+SSZ+HCQ n=178 (not all analysed)	24 weeks	(scale 0-10) 5.43 (2.20)	3.51 (2.19)	NR	(scale 0-100) 60.14 (22.98)	35.70(22.18)	NR
	ETN50 + MTX n=175 (not all		5.63 (1.95)	3.18 (2.32)	NR	61.06 (20.01)	35.35(24.43)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
	analysed)							
RACAT	MTX + SSZ + HCQ n=178 (not all analysed) some switched	48 weeks n=310 both groups	(scale 0-10) 5.43 (2.20)	3.01 (2.33)	NR	(scale 0-100) 60.14 (22.98)	32.87 (25.07)	NR
	ETN50 + MTX n=175 (not all analysed) some switched		5.63 (1.95)	2.98 (2.38)	NR	61.06 (20.01)	30.77 (23.05)	NR
APPEAL	MTX plus DMARD (SSZ, HCQ or LEF)	16 weeks	6.5 (1.8)	4.5	30.6	6.6 (1.8)	3.6	45.0
	ETN + MTX	16 weeks	6.7 (2.0)	3.3	50.8	6.6 (1.7)	2.5	62.1
Weinblatt 1999	PBO + MTX	24 weeks	(0-10 scale) 6.0 [c]	(0-10 scale) 4.0 [c]	NR	(0-10 scale) 6.5 [c]	(0-10 scale) 4.0 [c]	NR
	ETN + MTX	24 weeks	(0-10 scale) 6.0 [c]	(0-10 scale) 2.0 [a, c]	NR	(0-10 scale) 6.0 [c]	(0-10 scale) 2.0 [a, c]	NR
GO-FORWA	PBO + MTX	Week 14	(0-10 scale) 5.30 (3.70, 7.20) [c]	NR	- 14.6 (+10.8, -	(0-10 scale)	NR	- 34.9 (+2.4, -

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
RD					50.0) [c]	5.65 (4.30 to 6.85) [c]		64.6) [c]
	GOL + MTX	Week 14	(0-10 scale) 6.00 (3.80 to 7.90) [c]	NR	- 45.3 (-16.7, -76.9) [b, c]	(0-10 scale) 6.10 (5.10 to 7.10) [c]	NR	- 54.5 (-35.2, -72.9) [b, c]
GO-FORWARD	PBO + MTX	Week 24	(0-10 scale) 5.30 (3.70, 7.20) [c]	NR	- 17.3 (+16.3, -46.0) [c]	(0-10 scale) 5.65 (4.30 to 6.85) [c]	NR	- 39.1 (-1.3, -67.3) [c]
	GOL + MTX	Week 24	(0-10 scale) 6.00 (3.80 to 7.90) [c]	NR	- 47.9 (-17.0, -76.1) [b, c]	(0-10 scale) 6.10 (5.10 to 7.10) [c]	NR	- 61.7 (-38.7, -82.1) [b, c]
ATTRACT	PBO + MTX	30 weeks	(0-10 scale) 6.2 (4.3, 8.1) [c]	(0-10 scale) 5.5 (3.1, 7.5) [c]	- 7	(0-10 scale) 6.5	(0-10 scale) 5.0	- 13

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
						(5.2, 7.4) [c]	(3.0, 7.0) [c]	
	IFX + MTX	30 weeks	(0-10 scale) 6.6 (4.9, 7.8) [c]	(0-10 scale) 3.6 (1.8, 6.7) [c]	- 23 [a]	(0-10 scale) 6.1 (4.8, 7.1) [c]	(0-10 scale) 2.6 (1.5, 5.2) [,c]	- 53 [b]
Durez 2004	MP + MTX	14 weeks	63 (19-100) [c]	50 [e]	NR	58 (18-83) [c]	59 [e]	NR
	IFX + MTX	14 weeks	52 (15-80) [c]	42 [e]	NR	43 (14-85) [c]	16 [b,e]	NR
Wong 2009	PBO + MTX	Week 16	70 (25)	68 [e]	NR	NR	NR	NR
	IFX + MTX	Week 16	68 (15)	32 [a ,e]	NR	NR	NR	NR
ACT-RAY	TCZ + oral PBO	Week 24	NR	NR	Mean change (SD) = -32.4 (24.34)	NR	NR	Mean change (SD) = -38.5 (21.65)
	TCZ + MTX	Week 24	NR	NR	Mean change (SD) = -34.3	NR	NR	Mean change (SD) = -40.7

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Patient's global assessment of disease activity at baseline [d]	Patient's global assessment of disease activity at follow-up [d]	% change from baseline	Evaluator's global assessment of disease activity at baseline [d]	Evaluator's global assessment of disease activity at follow-up [d]	% change from baseline
					(25.68)			(19.55)
SATORI [362]	PBO + MTX	24 weeks	57 [e]	47 [e]	NR	60 [e]	47 [e]	NR
	TCZ + PBO capsules	24 weeks	60 [e]	28 [e]	NR	63 [e]	22 [e]	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] = *P<0.05*
[b] = *P<0.001*
[c] =*Median (IQR)*
[d] = *Reported on 0-100 VAS scale unless otherwise stated*
[e] = *Estimated from graphical data*

Table 368: Radiographic score data: Population 1 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Scoring system applied	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from BL in total score	Mean (SD) change from BL in erosion score	Mean (SD) change from BL in joint space narrowing score (JSN)	Radiographic non-progression
GUEPARD	van der Heijde-modified Sharp score data	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28 (N=29)	52 weeks	(score range of 0–448) 1.8 (4.7)	NR	NR	% patients with no radiographic progression = 55 (16/29)
		Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28 (N=27)	52 weeks	1.9 (4)	NR	NR	% patients with no radiographic progression = 59 (16/27)
OPTIMA	Van der Heijde modified Total Sharp Score	PBO + MTX (N=517, N=514 analysed for ΔmTSS)	26 weeks	0.96 (SD NR)	0.48 (SD NR)	0.48 (SD NR)	(ΔmTSS ≤0.5) 72%
		ADA + MTX (N=515, N=508 analysed for ΔmTSS)	26 weeks	0.15 [b] (SD NR)	0.10 [b] (SD NR)	0.05 [b] (SD NR)	87% [b]

PREMIER	van der Heijde modified TSS	PBO + MTX (N=257)	1 year	(0-398, with higher scores indicating greater progression) 5.7 worse	(scale NR, higher scores indicate worse erosion) 3.7 worse	(scale NR, higher scores indicate worse joint space narrowing) 2.0 worse	(change in mTSS ≤0.5 from baseline) 37%
		ADA mon + PBO (N=274)	1 year	3.0 worse	1.7 worse	1.3 worse	51% [a] (vs. MTX mon)
		ADA + MTX (N=268)	1 year	1.3 worse [b] (vs. MTX mon, vs. ADA mon)	0.8 worse [b] (vs. MTX mon, vs. ADA mon)	0.5 worse	64% [a] (vs. MTX mon, vs. ADA mon)
PREMIER	van der Heijde modified TSS	PBO + MTX (N=257)	2 years	10.4 worse	6.4 worse	4.0 worse	34%
		ADA mon + PBO (N=274)	2 years	5.5 worse	3.0 worse	2.6 worse	45% [a] (vs. MTX mon)
		ADA + MTX (N=268)	2 years	1.9 worse [b] (vs. MTX mon, vs. ADA mon)	1.0 worse [b] (vs. MTX mon, vs. ADA mon)	0.9 worse	61% [a] (vs. MTX mon, vs. ADA mon)
COMET	Van der Heijde-modified Total Sharp Score	PBO + MTX (N=230)	52 weeks	(Mean and 95% CI) 2.44 (1.45 to 3.43)	NR	NR	(defined as mTSS of 0.5 or less) 135/230 (59%)
		ETN + MTX (N=246)	52 weeks	(Mean and 95% CI) 0.27 (- 0.13 to 0.68)	NR	NR	196/246 (80%)

ERA	Total modified Sharp score	PBO + MTX (n=217)	6 months	(mTSS, 0 (no damage) to 398 (severe joint destruction) scale) 1.06 (worse)	(Erosion score, 0 (no new erosion) to 230 (new erosion, worsening of erosion)) 0.65 (worse) [d]	(JSN score, 0 (no narrowing) to 168 (complete loss of joint space)) 0.35 (worse) [d]	NR
		ETN + PBO (n=207)	6 months	0.57 [b] (worse)	0.25 [a, d] (worse)	0.2 (worse)	NR
ERA	Total modified Sharp score	PBO + MTX (n=217)	12 months	1.59 (worse)	1.0 (worse) [d]	0.55 (worse) [d]	NR
		ETN + PBO (n=207)	12 months	1.00 (worse)	0.45 [a, d] (worse)	0.55 (worse)	NR
ASPIRE	van der Heijde-modified Sharp score data	PBO + MTX (N=282 for total score, N=226 for erosion and JSN scores)	54 weeks	(scale 0 to 448, higher score = more joint damage) 3.7 (9.6), 0.43 [c] (0.0, 4.5)	(scale 0 to 280) 3.0 (7.8) 0.3 [c] (0.0, 3.8)	(scale 0 to 168) 0.6 (2.1) 0.0 [c] (0.0, 0.4)	NR
		IFX + MTX (N=359 for total score, N=306 for erosion and JSN scores)	54 weeks	0.4 (5.8) 0.0 [c] (-0.8, 1.3) [b]	0.3 (4.9) 0.0 [c] (-0.8, 1.3) [b]	0.1 (1.6) 0.0 [c] (0.0, 0.0) [b]	NR

[a] *< 0.05*
[b] *< 0.001*
[c] *= Median*
[d] *= estimated from graphical data*

Table 369: Assessments of synovitis, erosion and osteitis: Population 1 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean change from BL in synovitis (SD)	Mean change from BL in erosions (SD)	Mean change from BL in osteitis (SD)
OPTIMA Peterfy *et al.*, 2010 [364]	PBO + MTX (N=32)	26 weeks	OMERACT-RAMRIS scoring system. Progression or improvement of MRI scores defined as positive or negative change from baseline ≥ smallest detectable change (SDC) respectively - 2.0 (improved) % patients showing progression = 6 % patients showing improvement = 44	OMERACT-RAMRIS scoring system 1.4 (worse) % patients showing progression = 38 % patients showing improvement = 9	OMERACT-RAMRIS scoring system. 0.0 % patients showing progression = 13 % patients showing improvement = 9
	ADA + MTX (N=27)	26 weeks	- 3.6 (improved) % patients showing progression = 0 % patients showing improvement = 74 [a]	- 0.8 (improved) % patients showing progression = 4 [a] % patients showing improvement = 22	- 4.0 (improved) % patients showing progression = 0 % patients showing improvement = 30

GO-BEFORE [365]	PBO + MTX (synovitis N=81 wrists + MCP joint, N=82 wrist joints only, osteitis and erosion N=82)	24 weeks	(RAMRIS scores (higher RAMRIS scores = more severe inflammation/damage)) Wrist + MCP joints (range 0-21) Mean = - 1.04 (3.04) Median (IQR) = - 1.00 (- 1.63, 0.00) Wrist joints only (range 0-9) Mean = -0.74 (1.86) Median (IQR) = - 0.50 (-1.00, 1.00)	(RAMRIS scores) (range 0-230) - 0.24 (6.39) 0.00 [c] (0.00, 0.50)	(RAMRIS scores oedema (osteitis) (range 0-69)) - 0.32 (4.66) 0.00 [c] (- 1.50, 1.00)
	GOL + MTX (synovitis N=77 wrists + MCP joint, N=78 wrist joints only, osteitis and erosion N=78)	24 weeks	Wrist + MCP joints (range 0-21) - 2.21 (3.10) - 1.50 (- 3.50, - 0.33) [a,c] Wrist joints only (range 0-9) - 1.29 (1.67) - 1.00 (- 2.50, 0.00) [a,c]	(range 0-230) - 0.65 (5.98) 0.00 (- 0.58, 0.00) [a,c]	oedema (osteitis) (range 0-69) - 2.47 (4.08) - 1.00 (-3.00, 0.00) [a,c]

[a] *< 0.05*
[b] *< 0.001*
[c] *= Median*
[d] *= estimated from graphical data*

Table 370: Radiographic score data: Population 2/3 head to head biologic RCTs

Trial name / Author, year	Scoring system applied	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from BL in total score	Mean (SD) change from BL in erosion score	Mean (SD) change from BL in joint space narrowing score	Radiographic non-progression
AMPLE	Modified Sharp/van der Heijde scoring system	ABT s.c. (n=318, 91.1% assessed for radiographic non-progression)	1 year	(Scale 0-448, direction NR) 0.58 (3.22)	(Scale and direction NR) 0.29 (1.84)	(Scale and direction NR) 0.28 (1.92)	(change from BL in total score ≤ SDC at cut-off 2.8) 84.8%
		ADA (n=328, 88.1% assessed for radiographic non-progression)	1 year	0.38 (5)	- 0.01 (2.83)	0.39 (2.50)	88.6%

[a] *< 0.05*
[b] *< 0.001*
[c] *= Median*
[d] *= estimated from graphical data*

Table 371: Radiographic score data: Population 2/3 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Scoring system applied	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from BL in total score	Mean (SD) change from BL in erosion score	Mean (SD) change from BL in joint space narrowing score	Radiographic non-progression
AIM	Total Genant-modified Sharp score	PBO + MTX (N=195)	1 year	2.32 (SD NR) 0.53 (0.0, 2.5) [c]	1.14 (SD NR) 0.27 (0.0, 1.3) [a]	1.18 (SD NR) 0.0 (0.0, 1.0) [a]	NR
		ABT i.v.+ MTX (N=391)	1 year	1.21 (SD NR) 0.25 (0.0, 1.8) [a, c]	0.63 (SD NR) 0.0 (0.0, 1.0) [a]	0.58 (SD NR) 0.0 (0.0, 0.5) [a, c]	NR
DE019	Total Sharp score	PBO + MTX (N=200)	52 weeks	2.7 (6.8)	1.6 (4.4)	1.0 (3.0) % patients with improvement or no change in JSN = 52.2	NR
		ADA + MTX (N=207)	52 weeks	0.1 (4.8) [b]	0.0 (2.8) [b]	0.1 (2.3) [a] % patients with improvement or no change in JSN = 68.5 [a]	NR
JESMR	van der Heijde-modified Sharp score	ETN mon (N=71)	24 weeks	(0-448, positive score indicates progression) 2.57 (SD NR)	(Scale NR, positive value indicates progression) 1.16 (SD NR)	(Scale NR, positive value indicates progression) 1.42 (SD NR)	NR

		ETN + MTX (N=76)	24 weeks	0.34 (SD NR)	- 0.02 (SD NR)	0.37 (SD NR)	NR
JESMR	van der Heijde-modified Sharp score	ETN mon (N=71)	52 weeks	3.6 (SD NR)	1.87 (SD NR)	1.78 (SD NR)	No radiographic progression to week 52 (change ≤ 0.5) = 39.6% No clinically significant radiographic progression to week 52 (≤ smallest detectable change) = 58.5%
		ETN + MTX (N=76)	52 weeks	0.8 (SD NR)	- 0.15 (SD NR) [a]	1.01 (SD NR)	No radiographic progression to week 52 (change ≤ 0.5) = 57.4% No clinically significant radiographic progression to week 52 (≤ smallest detectable change) = 67.6%
LARA	Modified total Sharp score	MTX + DMARD (N=119)	24 weeks	adjusted mean change (SE) = 1.4 (0.5)	adjusted mean change (SE) = 1.1 (0.3)	adjusted mean change (SE) = 0.2 (0.3)	% patients with change ≤ 0 = 68.1

		ETN + MTX (N=247)	24 weeks	adjusted mean change (SE) = 0.4 (0.4) [a]	adjusted mean change (SE) = 0.4 (0.2) [a]	adjusted mean change (SE) = -0.1 (0.2)	% patients with change ≤ 0 = 75.3
RACAT	van der Heijde-modified Sharp score	MTX + SSZ + HCQ (N=158)	24 weeks	0.42 (1.91)	0.23 (1.32)	0.19 (1.25)	NR
		ETN50 + MTX (N=160)	24 weeks	0.003 (0.62)	- 0.03 (0.44)	0.03 (2.47)	NR
RACAT	van der Heijde-modified Sharp score	MTX + SSZ + HCQ (N=151)	48 weeks	0.54 (1.93)	0.29 (1.35)	0.25 (1.18)	NR
		ETN50 + MTX (N=153)	48 weeks	0.29 (3.32)	0.08 (1.48)	0.21 (2.09)	NR
GO-FORTH	van der Heijde-modified Sharp score	PBO + MTX (N=88)	24 weeks	Scale NR, positive value indicates greater progression 2.51 (5.52)	Scale NR, positive value indicates greater progression 1.66 (3.73) (N=84)	Scale NR, positive value indicates greater progression 0.83 (2.31) (N=84)	(No increase in totalvdH-Sharp score, i.e. change from baseline to week 24 <0) 44/88 (50.0%)
		GOL + MTX (N=66)	24 weeks	1.05 (3.71) [a]	0.54 (1.62) [a] (N=81)	0.71 (2.91) (N=81)	51/86 (59.3%)

ATTRACT [139]	van der Heijde-modified Sharp score	PBO + MTX (N=64)	54 weeks	(total scores range 0 to 440, higher scores indicating more joint damage) 7.0 (10.3)	(erosion scores range 0 to 280) 4.0 (7.9)	(JSN scores range 0 to 160) 2.9 (4.2)	Major progression (% patients) = 31 Improvement (% patients) = 14
		IFX + MTX (N=71)	54 weeks	1.3 (6.0) [b]	0.2 (2.9) [b]	1.1 (4.4) [b]	Major progression (% patients) = 8 [b] Improvement (% patients) = 44 [b]
Swefot [140]	van der Heijde-modified Sharp score	SSZ + HCQ + MTX (N=109)	24 months from baseline (i.e. 20-21 months post-randomisation)	Treatment difference (95% CI) = 3.23 (0.14 to 6.32) [a]	Treatment difference (95% CI) = 1.53 (- 0.03 to 3.09) [a]	Treatment difference (95% CI) =1.66 (- 0.14 to 3.46) [a]	NR
		IFX + MTX (N=106)	24 months from baseline (i.e. 20-21 months post-randomisation)				NR
ACT-RAY	Total Genant-modified Sharp score	TCZ + oral PBO (N=276)	24 weeks	0.22 (1.11)	0.11 (0.63)	0.11 (0.70)	% patients with no radiographic progression (change in score ≤ 0) = 58.7
		TCZ + MTX (N=277)	24 weeks	0.08 (1.88)	- 0.01 (0.78)	0.08 (1.48)	% patients with no radiographic progression (change in score ≤ 0) = 65.3

ACT-RAY [146]	Total Genant-modified Sharp score	TCZ + oral PBO (N=276)	52 weeks	0.63 (SD NR)	NR	NR	% patients with no radiographic progression (change in score ≤ 0) = 57.6
		TCZ + MTX (N=276)	52 weeks	0.40 (SD NR)	NR	NR	% patients with no radiographic progression (change in score ≤ 0) = 67.5
SAMURAI	Modified Total Sharp score (no further detail)	cDMARDs (N=143)	52 weeks	Mean (95% CI) 6.1 (4.2 to 8.0)	Mean (95% CI) 3.2 (2.1 to 4.3)	Mean (95% CI) 2.9 (2.0 to 3.8)	(change from baseline in TSS (0.5)) 39%
		TCZ (N=157)	52 weeks	2.3 (1.5 to 3.2) [a]	Mean (95% CI) 0.9 (0.3 to 1.4 [b]	Mean (95% CI) 1.5 (0.9 to 2.1 [a]	56% [a]

[a] *< 0.05*
[b] *< 0.001*
[c] *= Median*
[d] *= estimated from graphical data*

Table 372: Assessments of synovitis, erosion and osteitis: Population 2/3 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean change from BL in synovitis	Mean change from BL in erosions	Mean change from BL in osteitis
ASSET	PBO + MTX (N=23)	4 months	(OMERACT RAMRIS scores) adjusted mean change (wrists) (SE) = 0.38 (0.27)	(OMERACT RAMRIS scores) adjusted mean change (wrist and hand) (SE) = 0.95 (0.45)	(OMERACT RAMRIS scores) adjusted mean change (wrist and hand) (SE) = 1.54 (0.90)
	ABT i.v. + MTX (N=25)	4 months	adjusted mean change (wrists) (SE) = - 0.31 (0.26)	adjusted mean change (wrist and hand) (SE) = 0.45 (0.43)	adjusted mean change (wrist and hand) (SE) = - 1.94 (0.86)
GO-FORWARD [366]	PBO + MTX (N=72)	24 weeks	RAMRIS synovitis (wrist plus MCP) - 0.38 (2.66) - 0.50 (- 1.45, 1.00) [c] RAMRIS synovitis (wrist) 0.08 (1.51) 0.00 (- 1.00, 1.00) [c]	RAMRIS bone erosion score - 0.47 (3.40) 0.00 (- 0.50, 0.00) [c]	RAMRIS bone oedema (osteitis) score 0.71 (7.54) 0.00 (- 0.50, 0.50) [c]
	GOL + MTX (N=47)	24 weeks	RAMRIS synovitis (wrist plus MCP) - 1.85 (2.28) - 1.75 (- 3.00, - 0.50) [b, c] RAMRIS synovitis (wrist) - 1.13 (1.61) 1.00 (- 2.00, 0.00) [b, c]	RAMRIS bone erosion score - 1.08 (4.35) 0.00 (- 0.50, 0.00) [c]	RAMRIS bone oedema (osteitis) score Mean (SD)= - 2.58 (4.75) - 0.50 (- 4.09, 0.00) [b, c]

Durez 2007	MTX (N=14)	52 weeks	(OMERACT RAMRIS scores. Global synovitis score ranged from 0 (absence of synovitis) to 66 (severe synovitis)) (Mean change NR) Score at baseline = 21 (15-33) [d] Score at follow-up = 20 (12-24) [d]	(OMERACT RAMRIS scores. 0 (no erosion) to 300 (100% bone eroded) (Mean change NR) Score at baseline = 12 (8-25) [d] Score at follow-up = 14 (9-32) [d]	(OMERACT RAMRIS scores) (Mean change NR) Score at baseline = 13 (10-31) Score at follow-up = 13 (5-21)
	MTX + i.v. MP (N=15 randomised)	52 weeks	Score at baseline = 29 (17-33) [d] Score at follow-up = 14 (7-29) [d]	Score at baseline = 5 (3-23) [d] Score at follow-up = 13 (5-41) [d]	Score at baseline = 22 (7-40) [d] Score at follow-up = 12 (6-38) [d]
	IFX + MTX (N=15 randomised)	52 weeks	Score at baseline = 25 (15-29) [d] Score at follow-up = 10 (6-12) [d]	Score at baseline = 9 (5-11) [d] Score at follow-up = 11 (6-21) [d]	Score at baseline = 25 (12-32) [d] Score at follow-up = 11 (7-16) [d]

[a] *< 0.05*
[b] *< 0.001*
[c] *= Median*
[d] *= estimated from graphical data*

Table 373: Pain VAS Population 1 biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean Pain VAS score at baseline, 0-100 (SD)	Mean Pain VAS score at follow-up, 0-100 (SD)	Pain VAS mean change from baseline (SD)	% change from baseline
OPERA [97]	MTX + PBO + steroid	12 months (primary endpoint and study RCT endpoint)	91	58 (13-92) [c]	20 (0-71) [c]	NR	NR
OPERA [97]	ADA + MTX + steroid	12 months (primary endpoint and study RCT endpoint)	89	63 (13-98) [c]	7 (0-64) [a,c]	NR	NR
OPTIMA [367]	MTX + PBO	26 weeks (study RCT endpoint)	517	65 (21)	NR	-15.6 (22.70) (n=513)	NR
OPTIMA	ADA + MTX	26 weeks (study RCT endpoint)	515	65 (21)	NR	-28.9 (26.61) [b] (n=513)	NR
PREMIER	MTX + PBO	1 year (primary endpoint)	256	59.6 (24.3)	23.4 (16.1)	NR	NR
PREMIER	ADA monotherapy + PBO step up week 16	1 year (primary endpoint)	273	64.6 (23.6)	26.6 (17.1)	NR	NR
PREMIER	ADA + MTX step up week 16	1 year (primary endpoint)	265	62.5 (21.3)	16.8 (15.7) [b (vs. MTX), d]	NR	NR
PREMIER	MTX + PBO	2 years (study RCT endpoint)	256	59.6 (24.3)	12.5 (15.8)	NR	NR
PREMIER	ADA monotherapy + PBO step up week 16	2 years (study RCT endpoint)	273	64.6 (23.6)	19.6 (16.6)	NR	NR
PREMIER	ADA + MTX step up week 16	2 years (study RCT endpoint)	265	62.5 (21.3)	9.6 (14.9) [b (vs. MTX), d]	NR	NR
COMET Kekow 2010	MTX +PBO	week 52	263	65.1 (20.8)	33.7 (27.5)	-31.4	NR
COMET	ETN+MTX	week 52	265	66.0(21.4)	24.1(24.2)	-41.9 [b]	NR
GO-BEFORE	PBO + MTX	24 weeks	160	(0-10 scale) 6.3 (2.12)	NR	NR	44.35 [c]
GO-BEFORE	GOL 50 mg s.c. every 4 weeks + MTX (	24 weeks	159	(0-10 scale) 6.4 (2.11)	NR	NR	52.15 [a, c]
BeST [363]	Sequential monotherapy (DAS-steered)	6 months	NR	53.1 (SD NR)	NR	- 17.4	NR
BeST	Step-up combination therapy (DAS-steered)	6 months	NR	53.4 (SD NR)	NR	- 25.5	NR
BeST	Initial combination therapy with prednisone (DAS-steered)	6 months	NR	54.1 (SD NR)	NR	- 30.3 [a]	NR
BeST	Initial combination	6 months	NR	54.1 (SD NR)	NR	- 30.2	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean Pain VAS score at baseline, 0-100 (SD)	Mean Pain VAS score at follow-up, 0-100 (SD)	Pain VAS mean change from baseline (SD)	% change from baseline
	therapy with IFX (DAS-steered)					[a]	

[a] = p<0.05
[b] = p<0.01
[c] = Median (5th, 95th centile range)
[d] = Mixed model repeated measures analyses

Table 374: Pain VAS Population 2/3 biologic Head to head

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean Pain VAS score at baseline, 0-100 (SD)	Mean Pain VAS score at follow-up, 0-100 (SD)	Pain VAS mean change from baseline (SD)	% change from baseline
AMPLE	ABT s.c.	1 year (primary endpoint)	318	63.1 (22.3)	NR	NR	53
AMPLE	ADA	1 year (primary endpoint)	328	65.5 (21.8)	NR	NR	39.2
DeFilippis 2006	ETN + MTX	22 weeks	15	60.67 (16.57)	NR	NR	28.6
DeFilippis 2006	IFX + MTX	22 weeks	15	70.10 (14.14)	NR	NR	22
DeFilippis 2006	ETN + MTX	54 weeks	15	60.67 (16.57)	77.54	NR	43.06
DeFilippis 2006	IFX + MTX	54 weeks	15	70.10 (14.14)	87.75	NR	21.1

Table 375: Pain VAS Population 2/3 biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean Pain VAS score at baseline, 0-100 (SD)	Mean Pain VAS score at follow-up, 0-100 (SD)	Pain VAS mean change from baseline (SD)	% change from baseline
AIM	MTX+PBO	12 months	219	65.9 (20.6)	NR	adjusted -24.2(1.72)	NR
AIM	ABTi.v.+ MTX	12 months	433	63.3 (21.1)	NR	adjusted -35.8(1.12)	NR
ASSURE	PBO + cDMARDs	1 year (primary endpoint and study RCT endpoint)	413	61.3 (20.8) (n=418)	NR	NR	18
ASSURE	ABT + cDMARDs	1 year (primary endpoint and study RCT endpoint)	845	61.1 (20.4) (n=856)	NR	NR	37
CHANGE	PBO n=87	24weeks	87	62.7 (22.8)	NR	3.5 (25.4)	NR
CHANGE	ADAmon n=91	24weeks	91	68.1 (21)	NR	-17.4(27.9) [a]	NR
DE019	MTX+PBO n=200	52weeks	200	56.3(22.9)	NR	-11.2 (27.7)	-19.9%
DE019	ADA+MTX n=207	52weeks	207	55.9(20.4)	NR	-29.4(26.4)	-52.6%
van de Putte 2004	PBO s.c.	26 weeks	110	70.2 (18.1)	NR	- 11.0 (26.7)	- 11.4
van de Putte 2004	ADA 40mg s.c. eow monotherapy	26 weeks	113	70.3 (19.9)	NR	- 27.6 (31.1) ([b] vs. PBO)	- 37.7 ([b] vs. PBO)
ARMADA	MTX+PBO (n=62)	24 weeks	62	57.2 (21)	NR	-8.6 (22.5)	-15.0
ARMADA	ADA+MTX (n=67)	24 weeks	67	53 (22)	NR	-25.1 (33.1)	-47.2 [b]
Kim 2007	MTX+PBOrescueWeek18 n=63	24weeks	63	59.4(18.6)	NR	-7.3(27.5)	NR
Kim 2007	ADA+MTX n=65 (n=64 at 24weeks)	24weeks	64	57.6(18.2)	NR	-23.7(22.86) [b]	NR
CERTAIN [145]	PBO + cDMARDs	24 weeks (primary endpoint and study RCT endpoint)	98	NR	NR	[redacted]	NR
CERTAIN	CTZ 400mg at weeks 0, 2 & 4 then 200mg Q2W + DMARDs	24 weeks (primary endpoint and study RCT endpoint)	96	NR	NR	[redacted]	NR
ADORE	ETNmon n=159	16 weeks	140	62.7	NR	-29.40 (25.09)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean Pain VAS score at baseline, 0-100 (SD)	Mean Pain VAS score at follow-up, 0-100 (SD)	Pain VAS mean change from baseline (SD)	% change from baseline
ADORE	ETN+MTX n=155	16 weeks	135	63.3	NR	-29.93 (27.25)	NR
ETN Study 309 (Combe 2006)	SSZ+PBO n=50	24weeks	50	58.8(20)	NR	NR	13.3
ETN Study 309 (Combe 2006)	ETN+PBO n=103	24weeks	103	62.6(21.7)	NR	NR	55.6 [b] vs SSZ
ETN Study 309 (Combe 2006)	ETN+SSZ n=101	24weeks	101	58.5(20.7)	NR	NR	53.9 [b] vs SSZ non-sig vs ETN+PBO
JESMR	ETN 25mg Q2W monotherapy	24 weeks (primary endpoint)	69	NR	NR	NR	NR
JESMR	ETN 25mg Q2W + MTX 6-8mg/week	24 weeks (primary endpoint)	73	NR	NR	NR	NR
Lan 2004	PBO+MTX	12 weeks (primary endpoint and study RCT endpoint)	29	57.52	57.59	NR	0.05%
Lan 2004	ETN+MTX	12 weeks (primary endpoint and study RCT endpoint)	29	55.21	31.66 [a]	NR	43%
Moreland 1999	PBO	6months	80	(0-10 scale) 6.5	NR	NR	22 (worse)
Moreland 1999	ETN+PBO	6months	78	(0-10 scale) 6.7	NR	NR	-53 (improved) [b]
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178 (not all analysed)	24weeks	319 both groups	5.64(2.21)	3.64(2.38)	NR	NR
RACAT (O'Dell 2013)	ETN50+MTX n=175(not all analysed)	24weeks		5.88(1.99)	3.56(2.53)	NR	NR
RACAT (O'Dell 2013)	MTX+SSZ+HCQ n=178 randomised In analysis n=155 (of whom 39 switched to ETN)	48weeks	155	NR	3.22 (2.37)	NR	NR
RACAT (O'Dell 2013)	ETN50+MTX n=175 randomised In analysis n=155 (of whom 41 switched to MTX+SSZ+HCQ)	48weeks	155	NR	3.17 (2.58)	NR	NR
Weinblatt 1999	MTX +PBO	24weeks	30	(0-10 scale) 5.6 [c]	(0-10 scale) 4.4 [c]	NR	NR
Weinblatt 1999	ETN+ MTX, n=59	24weeks	59	(0-10 scale) 5.0 [c]	(0-10 scale) 1.8 [c b]	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	N analysed	Mean Pain VAS score at baseline, 0-100 (SD)	Mean Pain VAS score at follow-up, 0-100 (SD)	Pain VAS mean change from baseline (SD)	% change from baseline
APPEAL	MTX plus DMARD (SSZ, HCQ or leflunomide)	16 weeks (primary endpoint and study RCT endpoint)	103	60.8 (19.2)	38.6	NR	36.5
APPEAL	Etanercept 25mg twice weekly (licensed dose) plus MTX	16 weeks (primary endpoint and study RCT endpoint)	197	62.5 (23.4)	28.5 [b]	NR	54.4 [b]
GO-FORWARD	PBO s.c. every 4 weeks + MTX	Week 14	133	(0-10 scale) 5.70 (3.60 TO 7.50) [c]	NR	NR	17.6 (-8.1, 40.0) [c]
GO-FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	Week 14	89	(0-10 scale) 6.10 (4.70 to 7.70) [c]	NR	NR	55.0 (17.0, 76.5) [c] [b]
GO FORWARD	PBO s.c. every 4 weeks + MTX	Week 24	133	(0-10 scale) 5.70 (3.60 TO 7.50) [c]	NR	NR	15.4 (-16.4, 41.6) [c]
GO FORWARD	GOL 50 mg s.c. every 4 weeks + MTX	Week 24	89	(0-10 scale) 6.10 (4.70 to 7.70) [c]	NR	NR	50.4 (16.3, 83.3) [c b]
ATTRACT	PBO i.v. + MTX	30 weeks	88	(0-10 scale) 6.7 (5.0, 8.0) [c]	(0-10 scale) 5.9 (3.3, 7.4) [c]	NR	- 6
ATTRACT	IFX 3 mg/kg i.v. at weeks 0, 2 and 6 and every 8 weeks thereafter	30 weeks	86	(0-10 scale) 7.0 (5.6, 8.1) [c]	(0-10 scale) 3.8 (2.3, 6.9) [c]	NR	- 33 [a]
START	PBO + MTX	22 weeks (primary endpoint and study RCT endpoint)	363	(0-10 scale) 5.9 (5-7) [d]	NR	NR	NR
START	IFX 3mg/kg + MTX	22 weeks (primary endpoint and study RCT endpoint)	360	(0-10 scale) 6.1 (5-8) [d]	NR	NR	NR
ACT-RAY	TCZ 8 mg/kg i.v. every 4 weeks + oral PBO	Week 24	276	NR	NR	- 29.8 (24.92)	NR
ACT-RAY	TCZ 8 mg/kg i.v. every 4 weeks + MTX	Week 24	277	NR	NR	- 29.3 (26.64)	NR

[a] = $p<0.05$
[b] = $p<0.01$
[c] = Median (5th, 95th centile range)
[d] = Median (IQR)

Table 376: 0-100 VAS of fatigue: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (SD) change from baseline
COMET [368]	MTX	52 weeks	NR	NR	-19.7
	ETN + MTX	52 weeks	NR	NR	-29.6 [b]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *significant in a mixed-model repeated measures analysis*
[d] = *Adjusted mean change from baseline*
[e] = *Estimated from graphical data*

Table 377: FACIT-F score (0-52, greater scores indicate less fatigue): Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (SD) change from baseline	% change from baseline
OPTIMA [367]	MTX + PBO	26 weeks	NR	NR	8.3 (11.12)	NR
	ADA + MTX	26 weeks	NR	NR	10.5 (11.82) [a]	NR
PREMIER [369]	MTX + PBO	1 year	29.0 (11.1)	40.0 (8.10)	NR	NR
	ADA monotherapy + PBO step up week 16	1 year	26.2 (11.3) [a,c] (vs. MTX)	38.6 (8.0)	NR	NR
	ADA + MTX step up week 16	1 year	28.4 (11.7)	41.1 (8.2) [b (vs. MTX), c]	NR	NR
PREMIER [369]	MTX + PBO	2 years	29.0 (11.1)	42.5 (8.1)	NR	NR
	ADA monotherapy + PBO step up week 16	2 years	26.2 (11.3) [a,c] (vs. MTX)	40.8 (8.1)	NR	NR
	ADA + MTX step up week 16	2 years	28.4 (11.7)	43.0 (8.1) [b (vs. MTX), c]	NR	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *significant in a mixed-model repeated measures analysis*
[d] = *Adjusted mean change from baseline*
[e] = *Estimated from graphical data*

Table 378: 0-100 VAS of fatigue: Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (SD) change from baseline
AMPLE	ABT s.c. + MTX	1 year	NR	NR	-23.2
	ADA + MTX	1 year	NR	NR	-23.2

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *significant in a mixed-model repeated measures analysis*
[d] = *Adjusted mean change from baseline*
[e] = *Estimated from graphical data*

Table 379: FACIT-F score (0-52, greater scores indicate less fatigue): Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (SD) change from baseline	% change from baseline
ADACTA	TCZ 8 mg/kg i.v. every 4 weeks + s.c. PBO ADA	24 weeks	NR	NR	8.9 [d]	NR
	ADA 40 mg s.c. every 2 weeks + i.v. PBO TCZ	24 weeks	NR	NR	11.4 [d]	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *significant in a mixed-model repeated measures analysis*
[d] = *Adjusted mean change from baseline*
[e] = *Estimated from graphical data*

Table 380: 0-100 VAS of fatigue: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (SD) change from baseline
AIM [370]	MTX + PBO	1 year	63.5	NR	-22.6
	ABT + PBO	1 year	65.3	NR	-28.0 [a]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *significant in a mixed-model repeated measures analysis*
[d] = *Adjusted mean change from baseline*
[e] = *Estimated from graphical data*

Table 381: FACIT-F score (0-52, greater scores indicate less fatigue): Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (SD) change from baseline	% change from baseline
ARMADA	MTX+PBO	24weeks	NR	NR	3.0 improvement	NR
	ADA+MTX	24weeks	NR	NR	8.5 [a] improvement	NR
APPEAL [141]	MTX + DMARD (SSZ, HCQ or leflunomide)	16 weeks	30.1	33.2	NR	10.4
	ETN + MTX	16 weeks	28.1	36.2 [a]	NR	28.0 [a]
GO-FORWARD	PBO + MTX	Week 24	28.7 (10.5)	NR	2.16 (9.53)	NR
	GOL 50 mg + MTX	Week 24	26.6 (11.0)	NR	7.30 (8.65) [b]	NR
TOWARD	PBO + cDMARDs	24 weeks	NR	NR	3.6	NR
	TCZ 8 mg/kg i.v. + DMARDs	24 weeks	NR	NR	8.0 [b]	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *significant in a mixed-model repeated measures analysis*
[d] = *Adjusted mean change from baseline*
[e] = *Estimated from graphical data*

Table 382: 0-100 SF-36 components scores: Population 1 RCTs of biologic vs. DMARD(s) or PBO %$$**

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical component score (PCS) at baseline	Mean (SD) PCS at follow-up	Mean (SD) change from baseline in PCS	Mean (SD) mental component score (MCS) at baseline	Mean (SD) MCS at follow-up	Mean (SD) change from baseline in MCS	Mean (SD) arthritis-specific health index (ASHI) score at baseline	Mean (SD) ASHI at follow-up	Mean (SD) change from baseline in ASHI score
HIT HARD	MTX + PBO	24 weeks	31.7 (8.3)	39.8 (9.9)	NR	45.2 (10.2)	48.9 (8.8)	NR	NR	NR	NR
	ADA + MTX	24 weeks	28.3 (7.7) [a]	44.0 (11.1) [b]	NR	46.7 (9.9)	48.8 (9.8)	NR	NR	NR	NR
PREMIER [369]	MTX + PBO	1 year	32.2 (7.9)	43.5 (8.1)	NR	43.5 (12.4)	51.3 (8.5)	NR	NR	NR	NR
	ADA monotherapy + PBO step up week 16	1 year	30.7 (7.4)	42.5 (7.9)	NR	42.6 (12.1)	49.1 (8.2) [a,f]	NR	NR	NR	NR
	ADA + MTX step up week 16	1 year	31.7 (7.8)	46.6 (8.2) [b] (vs. MTX), f	NR	44.1 (12.5)	50.7 (8.7)	NR	NR	NR	NR
PREMIER [369]	MTX + PBO	2 years	32.2 (7.9)	45.9 (7.8)	NR	43.5 (12.4)	52.4 (8.4)	NR	NR	NR	NR

	ADA monotherapy + PBO step up week 16	2 years	30.7 (7.4)	44.7 (8.0)	NR	42.6 (12.1)	49.8 (8.1) [a] (vs. MTX), f	NR	NR	NR	NR
	ADA + MTX step up week 16	2 years	31.7 (7.8)	48.8 (8.3) [b] (vs. MTX), f	NR	44.1 (12.5)	51.8 (8.8)	NR	NR	NR	NR
COMET[368]	MTX	52 weeks	NR	NR	10.7	NR	NR	6.1	NR	NR	NR
	ETN + MTX	52 weeks	NR	NR	13.7 [a]	NR	NR	6.8	NR	NR	NR
ERA [371]	MTX + PBO	52 weeks	NR	NR	9.6 (0.8) [d]	NR	NR	4.1 (0.8) [d]	NR	NR	8.1 (1.0) [d]
	ETN 25mg Q2W + PBO	52 weeks	NR	NR	10.7 (0.8) [d]	NR	NR	3.6 (0.8) [d]	NR	NR	8.2 (1.0) [a,d]
ASPIRE	PBO i.v. + MTX	54 weeks	NR	NR	10.1 (11.4)	NR	NR	NR	NR	NR	NR
	IFX i.v. + MTX	54 weeks	NR	NR	11.7 (11.6)	NR	NR	NR	NR	NR	NR
BeST	Sequential monotherapy	6 months	NR	NR	8.0 [b] (vs. combi+pred & combi+IFX)	NR	NR	3.1	NR	NR	NR
	Step-up combination therapy	6 months	NR	NR	8.5 [b] (vs. combi+pred & combi+IFX)	NR	NR	3.5	NR	NR	NR

	Initial combination therapy with prednisone	6 months	NR	NR	12.5	NR	NR	1.2	NR	NR	NR
	Initial combination therapy with IFX	6 months	NR	NR	12.4	NR	NR	4.1	NR	NR	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 383: 0-100 SF-36 domains scores – baseline and follow-up: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical functioning (PF) score at baseline	Mean (SD) PF score at follow-up	Mean (SD) role-physical (RP) score at baseline	Mean (SD) RP score at follow-up	Mean (SD) bodily pain (BP) score at baseline	Mean (SD) BP score at follow-up	Mean (SD) general health (GH) score at baseline	Mean (SD) GH score at follow-up	Mean (SD) vitality (VT) score at baseline	Mean (SD) VT score at follow-up	Mean (SD) social functioning (SF) score at baseline	Mean (SD) SF score at follow-up	Mean (SD) role-emotional (RE) score at baseline	Mean (SD) RE score at follow-up	Mean (SD) mental health (MH) score at baseline	Mean (SD) MH score at follow-up
PREMIER [369]	MTX + PBO	1 year	31.5 (10.3)	41.8 (9.7)	32.6 (8.4)	44.1 (8.9)	32.7 (7.7)	46.5 (7.3)	40.5 (9.1)	46.4 (8.2)	40.6 (9.7)	51.8 (8.7)	38.1 (12.2)	47.9 (7.8)	36.7 (13.8)	46.2 (8.6)	42.6 (12.1)	50.0 (9.0)
	ADA monotherapy + PBO step up week 16	1 year	29.1 (9.5)	40.5 (9.0)	32.5 (8.1)	43.3 (8.0)	31.6 (7.8)	44.9 (6.9) [a,f]	39.8 (9.6)	45.4 (7.9) [a,f]	39.2 (9.4)	49.6 (8.3) [a,f]	35.2 (12.2)	45.9 (7.4) [a,f]	37.5 (13.9)	44.5 (7.9) [a,f]	41,4 (11.9)	48.0 (8.7)
	ADA + MTX step up week 16	1 year	30.2 (10.0)	44.7 (9.2) [b,f]	33.1 (8.8)	46.6.(8.2) [b,f]	32.5 (7.1)	49.7 (7.3) [b,f]	40.9 (10.0)	48.2 (8.2)	40.0 (10.0)	52.9 (8.8) [a,f]	38.3 (12.0)	48.7 (7.4)	38.4 (14.1)	47.3 (8.1)	42.1 (12.2)	49.9 (8.8)
PREMIER [369]	MTX + PBO	2 years	31.5 (10.3)	44.3 (9.3)	32.6 (8.4)	46.5 (8.6)	32.7 (7.7)	48.8 (7.1)	40.5 (9.1)	47.2 (8.2)	40.6 (9.7)	53.7 (8.5)	38.1 (12.2)	49.2 (7.6)	36.7 (13.8)	48.1 (8.0)	42.6 (12.1)	51.1 (9.3)
	ADA monotherapy + PBO step up week 16	2 years	29.1 (9.5)	43.0 (9.1)	32.5 (8.1)	45.5. (8.0)	31.6 (7.8)	47.1 (6.9) [a,f]	39.8 (9.6)	46.7 (8.1) [a,f]	39.2 (9.4)	51.4 (8.4) [a,f]	35.2 (12.2)	48.0 (7.6) [a,f]	37.5 (13.9)	45.8 (7.9) [a,f]	41,4 (11.9)	49.2 (8.7)
	ADA + MTX step up week 16	2 years	30.2 (10.0)	46.9 (9.2) [b,f]	33.1 (8.8)	48.8 (8.2) [b,f]	32.5 (7.1)	51.8 (7.2) [b,f]	40.9 (10.0)	49.5 (8.3)	40.0 (10.0)	54.7 (9.0) [a,f]	38.3 (12.0)	49.9 (7.4)	38.4 (14.1)	49.1 (7.8)	42.1 (12.2)	51.1 (8.7)

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 384: 0-100 SF-36 domains scores – mean change from baseline: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from baseline in physical functioning (PF) score	Mean (SD) change from baseline in role-physical (RP) score	Mean (SD) change from baseline in bodily pain (BP) score	Mean (SD) change from baseline in general health (GH) score	Mean (SD) change from baseline in vitality (VT) score	Mean (SD) change from baseline in social functioning (SF) score	Mean (SD) change from baseline in role-emotional (RE) score	Mean (SD) change from baseline in mental health (MH) score
ERA [371]	MTX + PBO	52 weeks	10.4 (0.8)	9.9 (0.9)	10.1 (0.7)	3.4 (0.7)	6.8 (0.8)	8.1 (0.9)	4.7 (1.0)	5.8 (0.8)
	ETN 25mg Q2W + PBO	52 weeks	9.7 (0.8)	10.8 (0.9)	10.5 (0.8)	4.5 (0.7)	7.9 (0.8)	8.4 (0.9)	4.0 (1.1)	4.4 (0.8)

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 385: 0-100 SF-12 components scores: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical component score (PCS) at baseline (0-100)	Mean (SD) PCS at follow-up (0-100)	Mean (SD) change from baseline in PCS (0-100)	Mean (SD) mental component score (MCS) at baseline (0-100)	Mean (SD) MCS at follow-up (0-100)	Mean (SD) change from baseline in MCS (0-100)
OPERA	MTX + PBO + steroid	12 months	31.7 (19.3-44.5) [c]	43.3 (26.1-55.8) [c]	10.6 (-11.26-22.7) [c]	46.7 (25.7-60.1) [c]	54.8 (40.4-65.7) [c]	4.3 (-9.3-27.4) [c]
	ADA + MTX + steroid	12 months	30.9 (13.1-50.6) [c]	49.2 (29.9-56.6) [a,c]	13.2 (-2.3-33.0) [a,c]	47.0 (28.6-60.6) [c]	55.7 (35.8-62.6) [c]	5.5 (-8.5-20.1) [c]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 386: 0-100 SF6D & RAQoL: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) SF6D score at baseline	Mean (SD) SF6D score at follow-up	Mean (SD) change from baseline in SF6D score	Mean (SD) RAQoL score at baseline	Mean (SD) RAQoL score at follow-up	Mean (SD) change from baseline in RAQoL score	% change from baseline in RAQoL score
Bejarano2008	PBO + MTX	56 weeks	NR	NR	NR	NR	NR	-4.7 (8.4)	NR
	ADA + MTX	56 weeks	NR	NR	NR	NR	NR	-7.6(7.4) [a]	NR
PREMIER [369]	MTX + PBO	1 year	0.56 (0.11)	0.72 (0.14)	NR	NR	NR	NR	NR
	ADA monotherapy + PBO step up week 16	1 year	0.54 (0.11)	0.70 (0.14) [a,f]	NR	NR	NR	NR	NR
	ADA + MTX step up week 16	1 year	0.45 (0.11)	0.75 (0.13) [a,f]	NR	NR	NR	NR	NR
PREMIER [369]	MTX + PBO	2 years	0.56 (0.11)	0.73 (0.14)	NR	NR	NR	NR	NR
	ADA monotherapy + PBO step up week 16	2 years	0.54 (0.11)	0.70 (0.13) [a,f]	NR	NR	NR	NR	NR
	ADA + MTX step up week 16	2 years	0.45 (0.11)	0.76 (0.14) [a,f]	NR	NR	NR	NR	NR
Quinn 2005	MTX + PBO	14 weeks	NR	NR	NR	NR	NR	NR	7 [f] (worse)

	IFX 3mg/kg + MTX	14 weeks	NR	NR	NR	NR	NR	NR	-74 [a,f] (improved)
Quinn 2005	MTX + PBO	54 weeks	NR	NR	NR	NR	NR	NR	0 [f]
	IFX 3mg/kg + MTX	54 weeks	NR	NR	NR	NR	NR	NR	-82 [a,f] (improved)

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 387: 0-100 EQ5D & EQ5D-NL: Population 1 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) EQ5D score at baseline (0-1)	Mean (SD) EQ5D score at follow-up (0-1)	Mean (SD) change from baseline in EQ5D score (0-1)
OPERA	MTX + PBO + steroid	12 months	0.64 (0.22-0.80) [c]	0.78 (0.49-1.00) [c]	0.20 (-0.06-0.56) [c]
	ADA + MTX + steroid	12 months	0.61 (0.17-0.80) [c]	0.82 (0.38-1.00) [a,c]	0.22 (-0.05-0.67) [c]
BeST [372]	Sequential monotherapy	6 months	0.5 [f]	0.65 [f]	NR
	Step-up combination therapy	6 months	0.5 [f]	0.6 [f]	NR
	Initial combination therapy with prednisone	6 months	0.5 [f]	0.75 [f]	NR
	Initial combination therapy with IFX	6 months	0.5 [f]	0.8 [f]	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 388: 0-100 SF-36 components scores: Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical component score (PCS) at baseline	Mean (SD) PCS at follow-up	Mean (SD) change from baseline in PCS	Mean (SD) mental component score (MCS) at baseline	Mean (SD) MCS at follow-up	Mean (SD) change from baseline in MCS
ATTEST	PBO + MTX	Day 197	NR	NR	4 [f]	NR	NR	1 [f]
	IFX + MTX	Day 197	NR	NR	7 [f]	NR	NR	4 [f]
	ABT + MTX	Day 197	NR	NR	8 [f]	NR	NR	5 [f]
AMPLE	ABT s.c. + MTX	1 year	NR	NR	9.37	NR	NR	3.92
	ADA + MTX	1 year	NR	NR	8.84	NR	NR	3.62
ADACTA	TCZ 8 mg/kg i.v. every 4 weeks + s.c. PBO ADA	24 weeks	NR	NR	9.2	NR	NR	7.9
	ADA 40 mg s.c. every 2 weeks + i.v. PBO TCZ	24 weeks	NR	NR	7.6	NR	NR	5.0 [a]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 389: 0-100 SF-36 domains scores – mean change from baseline: Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from baseline in physical functioning (PF) score	Mean (SD) change from baseline in role-physical (RP) score	Mean (SD) change from baseline in bodily pain (BP) score	Mean (SD) change from baseline in general health (GH) score	Mean (SD) change from baseline in vitality (VT) score	Mean (SD) change from baseline in social functioning (SF) score	Mean (SD) change from baseline in role-emotional (RE) score	Mean (SD) change from baseline in mental health (MH) score
AMPLE	ABT s.c. + MTX	1 year	7.92	8.87	10.67	5.44	5.84	7.33	6	4.21
	ADA + MTX	1 year	7.81	7.91	10.65	5.26	5.51	6.5	5.84	3.86

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 390: 0-100 EQ-5D utility score: Population 2/3 biologic head-to-head RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) EQ5D score at baseline (0-1)	Mean (SD) EQ5D score at follow-up (0-1)	Mean (SD) change from baseline in EQ5D score (0-1)
RED-SEA	ADA n=60	12 months	0.52 (0.06–0.66)	0.59 (0.52–0.69)	NR
	ETN n=60	12 months	0.52 (0.06–0.69)	0.59 (0.24–0.73)	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 391: 0-100 SF-36 components scores: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical component score (PCS) at baseline	Mean (SD) PCS at follow-up	Mean (SD) change from baseline in PCS	% change from baseline in PCS	Mean (SD) mental component score (MCS) at baseline	Mean (SD) MCS at follow-up	Mean (SD) change from baseline in MCS	% change from baseline in MCS
AIM Russell 2007	MTX + PBO	1 year	30.7 (7.5)	35 [f]	NR	NR	40.8 (11.2)	46 [f]	NR	NR
	ABT + PBO	1 year	30.6 (7.3)	40 [b,f]	NR	NR	41.8 (11.4)	49 [a,f]	NR	NR
CERTAIN Clinicaltrials.gov (NCT00674362)	PBO + cDMARDs	24 weeks	NR	NR	1.7 (5.6)	NR	NR	NR	0.5 (9.6)	NR
	CTZ + cDMARDs	24 weeks	NR	NR	6.0 (7.50)	NR	NR	NR	4.0 (9.77)	NR
APPEAL [141]	MTX + DMARD (SSZ, HCQ or leflunomide)	16 weeks	30.1	37.3	NR	22.8 improvement	42.4	47.8	NR	13.3 improvement
	ETN + MTX	16 weeks	30.5	40.4 [b]	NR	31.4 [b] improv	42.9	50.2 [a]	NR	17.5 [a] improv

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical component score (PCS) at baseline	Mean (SD) PCS at follow-up	Mean (SD) change from baseline in PCS	% change from baseline in PCS	Mean (SD) mental component score (MCS) at baseline	Mean (SD) MCS at follow-up	Mean (SD) change from baseline in MCS	% change from baseline in MCS
						ement				ement
GO-FORWARD	PBO + MTX	Week 24	NR	NR	2.54 (8.06) improvement	NR	NR	NR	0.75 (9.68) improvement	NR
	GOL 50 mg + MTX	Week 24	NR	NR	8.28 (8.33) [b] improvement	NR	NR	NR	1.83 (10.87) improvement	NR
ATTRACT [179]	PBO i.v. + MTX	54 week	NR	NR	NR	NR	NR	NR	NR	9 improvement
	IFX i.v. mon	54 week	NR	NR	NR	NR	NR	NR	NR	34 [b] improvement
TOWARD	PBO + cDMARDs	24 weeks	NR	4.1 improvement	NR	NR	NR	2.3 improvement	NR	NR
	TCZ 8 mg/kg i.v. + DMARDs	24 weeks	NR	8.9 [b] improvement	NR	NR	NR	5.3 [b] improvement	NR	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	NR

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical component score (PCS) at baseline	Mean (SD) PCS at follow-up	Mean (SD) change from baseline in PCS	% change from baseline in PCS	Mean (SD) mental component score (MCS) at baseline	Mean (SD) MCS at follow-up	Mean (SD) change from baseline in MCS	% change from baseline in MCS
			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	NR

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 392: 0-100 SF-36 domains scores – baseline and follow-up: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) physical functioning (PF) score at baseline	Mean (SD) PF score at follow-up	Mean (SD) role-physical (RP) score at baseline	Mean (SD) RP score at follow-up	Mean (SD) bodily pain (BP) score at baseline	Mean (SD) BP score at follow-up	Mean (SD) general health (GH) score at baseline	Mean (SD) GH score at follow-up	Mean (SD) vitality (VT) score at baseline	Mean (SD) VT score at follow-up	Mean (SD) social functioning (SF) score at baseline	Mean (SD) SF score at follow-up	Mean (SD) role-emotional (RE) score at baseline	Mean (SD) RE score at follow-up	Mean (SD) mental health (MH) score at baseline	Mean (SD) MH score at follow-up
Durez 2004	MP + MTX	14 weeks	27 (26)	24 (26)	13 (28)	35 (41)	26 (16)	32 (24)	26 (19)	29 (22)	27 (20)	29 (22)	44 (16)	40 (25)	22 (39)	39 (47)	45 (21)	45 (22)
	IFX + MTX	14 weeks	36 (22)	55 (23) [a]	42 (48)	45 (42)	35 (23)	52 (16)	40 (16)	50 (16) [a]	31 (25)	45 (20)	53 (30)	66 (22) [a]	58 (47)	67 (42)	52 (25)	60 (23)
[redacted]																		

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 393: 0-100 SF-36 domains scores – mean change from baseline: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from baseline in physical functioning (PF) score	Mean (SD) change from baseline in role-physical (RP) score	Mean (SD) change from baseline in bodily pain (BP) score	Mean (SD) change from baseline in general health (GH) score	Mean (SD) change from baseline in vitality (VT) score	Mean (SD) change from baseline in social functioning (SF) score	Mean (SD) change from baseline in role-emotional (RE) score	Mean (SD) change from baseline in mental health (MH) score
CERTAIN Clinical trials.gov (NCT00674362)	PBO + cDMARDs	24 weeks	0.4 (8.90)	1.7 (7.81)	2.8 (8.50)	0.9 (8.06)	0.6 (8.41)	0.8 (8.89)	-0.2 (12.33)	1.2 (7.72)
	CTZ + cDMARDs	24 weeks	5.1 (7.36)	4.7 (9.77)	8.0 (8.70)	5.0 (7.59)	6.4 (8.74)	4.3 (10.21)	3.2 (13.74)	5.2 (8.43)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*

[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 394: 0-100 EQ5D: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) EQ5D score at baseline (0-1)	Mean (SD) EQ5D score at follow-up (0-1)	Mean (SD) change from baseline in EQ5D score (0-1)	Mean (SD) change from baseline in EQ5D VAS (0-100)
ADORE van Riel 2006	ETNmon	16 weeks	NR	NR	0.1883 (0.33)	19.76 (27.24)
	ETN+MTX	16 weeks	NR	NR	0.2399 (0.32)	21.00 (26.61)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 395: 0-100 EQ5D domains scores – mean change form baseline: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) change from baseline in usual activities (0-1)	Mean (SD) change from baseline in self-care (0-1)	Mean (SD) change from baseline in pain / discomfort (0-1)	Mean (SD) change from baseline in mobility (0-1)	Mean (SD) change from baseline in anxiety / depression (0-1)
ADORE van Riel 2006	ETNmon	16 weeks	0.3077 (0.61)	0.1731 (0.55)	0.3718 (0.62)	0.3077 (0.50)	0.2323 (0.59)
	ETN+MTX	16 weeks	0.2867 (0.55)	0.3533 (0.55) [a]	0.4400 (0.65)	0.2318 (0.52)	0.24 (0.65)

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 396: 0-100 EuroQol VAS scores: Population 2/3 RCTs of biologic vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment point	Mean (SD) baseline score	Mean % change
ETN309	SSZ+PBO	24 weeks	44.6 (19.0)	20.1
	ETN+PBO	24 weeks	45.5 (21.3)	64.6 [a (vs. SSZ)]
	ETN+SSZ	24 weeks	43.1 (22.4)	67.6 [a (vs. SSZ)]

[a] = *P<0.05*
[b] = *P<0.001*
[c] = *Median (5th/95th percentile range)*
[d] = *Mean change from baseline (SE)*
[e] = *Adjusted mean change from baseline*
[f] = *Estimated from graphical data*
[g] = *significant in a mixed-model repeated measures analysis*
[h] = *Mean [95% CI]*

Table 397: Adverse events and discontinuations due to adverse events: Population 1 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
GUEPARD	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	RCT	52 weeks	NR	NR	5/32 (16) five patients were hospitalised for the following reasons: one for vasculitis with revision of diagnosis to Sharp syndrome (Week 6), one for hepatitis secondary to MTX (Week 4), one for a hip prosthesis operation (Week 12), one for weight loss (Week 36) and one for haemopthysis (Week 32).
	Initial ADA + MTX 12 weeks, then step-up therapy in both groups based on DAS28	RCT	52 weeks	NR	NR	5/33 (15) one had hepatitis (Week 6), the other had MTX pneumonia (Week 6) and the last had acoustic neuroma (Week 10) plus two malignancy
HIT HARD	PBO + MTX	RCT	24 weeks	4/85 (4.7)	NR	NR
	ADA + MTX	RCT	24 weeks	2/87 (2.3)	NR	NR
HIT HARD	PBO + MTX for 24 weeks followed by OL MTX for 24 weeks	LTE	48 weeks	7/85 (8.2)	NR	22/85 (25.8) 4 serious infections (2 urosepsis, 1 pneumonia), 1 stroke, 1 diplopia, 1 paresthesia, 3 caardiac disorders (1 bypass surgery, 1 claudication, 1 myocarditis), 1

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						reactive depression, 3 solid malignant tumours (1 prostate, 2 cervix), 1 peripheral artery angioplasty, 1 shoulder impingment syndrome, 1 prolapsed lumbar disc, 1 fracture, 3 arthritis flare, 1 nephrolithiasis
	ADA + MTX for 24 weeks followed by OL MTX for 24 weeks	LTE	48 weeks	4/87 (4.6)	NR	12/87 (13.8) 3 serious infections (1 bronchitis, 2 abscess), 1 concussion, 1 syncope, 1 benign neoplasm (prostate), 1 subileus, 1 gastric haemorrhage, 1 varicose veins, 1 vasculitis, 1 coxarthrosis, 1 fracture.
OPERA	PBO +MTX + steroid	RCT	12 months	1/91 (1.1)	NR	10/91 (11.0) 2 malignancies (1 urothelial carcinoma, 1 basocellular carcinoma), 3 serious infections (1 pneumonia, 1 bronchitis, 1 dental abscess), 2 fivefold increased serum alanine aminotransferase, 1 disease exacerbation, 1 leucopoenia, 1 polyneuropathia, 1 peptic ulcer, 1 coronary bypass, 1 hip fracture, 1 coxarthrosis. 1 patient who terminated due to non-compliance at 6 months died due to pneumonia 4 months later.

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	ADA + MTX + steroid	RCT	12 months	2/89 (2.2)	NR	14/89 (15.7) 3 malignancies (1 small cell lung carcinoma, 1 myelodysplastic syndrome, 1 basocellular carcinoma), 3 serious infections (1 empyema, 1 pneumonia, 1 bronchitis), 1 suspected but unconfirmed infectious arthritis, 1 local subcutaneous atrophy, 1 blurred vision, 1 acute myocardial infarction, 1 tachicardia, 1 gonarthrosis
OPTIMA	PBO + MTX	RCT	26 weeks	16/517 (3)	NR Infections in 36.4%.	NR 6 serious infections
	ADA + MTX	RCT	26 weeks	21/515 (4)	NR	NR 2 malignancies (1 malignant melanoma in situ, 1 squamous cell carcinoma), 13 serious infections, 1 case of lupus-like syndrome, no lymphoma or demyelinating disease.
PREMIER	PBO + MTX	RCT	2 years	19/257 (7.4)	245/257 (95.3)	7 serious infections (2 pneumonia, 1 septic arthritis, 1 sinusitis, 1 abscess, 1 bacteremia, 1 parotitis), 4 malignancies (lymphoma, melanoma, prostate, breast)
	ADA monotherapy +	RCT	2 years	26/274 (9.5)	262/274 (95.6)	3 serious infections (1 pneumonia, 1 cellulitis, 1 septic arthritis), 1 lupus-like

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	PBO					reaction, 4 malignancies (breast, colon, multiple myeloma, metastatic cancer with unknown primary site)
	ADA + MTX	RCT	2 years	32/268 (11.9)	262/268 (97.8)	9 serious infections (3 pulmonary infections (inc. 1 plaural TB)), 1 sinus infection, 1 wound infection, 1 septic arthritis, 1 infected hygroma, 1 cellulitis, 1 urinary tract infection), 2 malignancies (1 ovarian, 1 prostate)
PREMIER	PBO + MTX to OL ADA monotherapy	LTE	5 years	7.7%	NR	2/497 (0.4) During open-label period: 3.3 serious infections per 100 person years 2 TB, 1 lymphoma, 1 non-melanoma skin cancer, 3 breast cancer, 2 bladder cancer, 1 malignant melanoma, 1 tongue neoplasm, 1 pancreatic neoplasm, 1 lung cancer, 1 gastric cancer, 1 colon cancer. No lupus-like syndrome or demyelinating disease.
	ADA monotherapy + PBO to OL ADA monotherapy	LTE	5 years	10.7%	NR	
	ADA + MTX to OL ADA monotherapy	LTE	5 years	14.2%	NR	
COMET	PBO + MTX	RCT period 1, 52 weeks	52 weeks	34/268 (12.7)	246/268 (91·8)	34/268 (12·7) %s NR if less than 1% Cardiac 2 (1%) Eye n=1

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						Gastrointestinal 4 (1%) General and administration site n=1 Infection 8 (3%) Injury, poisoning, and procedural complications 4 (1%) Laboratory values n=1 Musculoskeletal and connective tissue 9 (3%) Nervous system n=1 Psychiatric n=1 Renal and urinary n=1 Respiratory, thoracic, and mediastinal 1 Surgical and medical procedures 2 (1%) Vascular 2 (1%) Malignancy n=4
	ETN + MTX	RCT period 1, 52 weeks	52 weeks	28/274 (10.2)	247/274 (90·2)	33/274 (12·0) Cardiac 2 (1%)) Ear and labyrinth 1 Gastrointestinal 1 General and administration site 2 (1%) Hepatobiliary 3 (1%) Infection 5 (2%) Injury, poisoning, and procedural

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						complications 3 (1%) Laboratory values 1 Metabolic and nutritional 2 (1%) Musculoskeletal and connective tissue 4 (1%) Nervous system 4 (1%) Psychiatric 1 Renal and urinary 1 Respiratory, thoracic, and mediastinal 3 (1%) Skin and subcutaneous tissue 1 Surgical and medical procedures 1 Vascular 1 Malignancy n=4
COMET Emery 2010 [135]	MTX in year 1 MTX in year 2	RCT period 2	weeks 52-104	NR	79/99 (79.8)	12/99 (12.1) 1 death 3 malignancies remainder serious infections
	MTX year 1 ETN+MTX in year 2	RCT period 2	weeks 52-104	NR	71/90 (78.9)	11/90 (12.2) 5 malignancies remainder serious infections
	ETN+MTX in	RCT	weeks 52-	NR	91/111 (82.0)	8/111 (7.2)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	year 1 ETN+MTX in year 2	period 2	104			serious infections
	ETN+MTX in year 1 ETN in year 2	RCT period 2	weeks 52-104	NR	89/111 (80.2)	10/111 (9.0) 1 malignancy rest serious infections
ERA	PBO + MTX	RCT	12 months	22/217 (10)	NR	NR 2 malignancies (bladder cancer, colon cancer). Infections requiring hospitalisation/intravenous antibiotics in <3%
	ETN + PBO	RCT	12 months	10/207 (5)	NR	NR 3malignancies (carcinoid lung cancer, Hodgkin's disease and prostate cancer) Infections requiring hospitalisation/intravenous antibiotics in <3%
ERA	PBO + MTX	LTE	2 years	27/217 (12)	NR	NR 9 patients had infections requiring hospitalisation/intravenous antibiotics 3 malignancies
	ETN + PBO	LTE	2 years	15/207 (7)	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						7 patients had infections requiring hospitalisation/intravenous antibiotics 4 malignancies
GO-BEFORE	PBO + MTX	RCT	24 weeks	2/160 (1.3)	116/160 (72.5)	11/160 (6.9) (NR for extracted treatment arm)
	GOL + MTX	RCT	24 weeks	6/158 (3.8)	129/158 (81.6)	10/185 (5.4) (NR for extracted treatment arm)
GO-BEFORE [136]	PBO + MTX	LTE	Week 104	NR	NR	N/A
	GOL + MTX	LTE	Week 104	NR	NR	13.7% (NR)
ASPIRE	PBO + MTX	RCT	54 weeks	9/298 (3.0)	NR	2/291 (0.7) (myocardial infarction)
	IFX + MTX	RCT	54 weeks	34/373 (9.1)	NR	16/372 (4.3) (pneumonia, myocardial infarction, asthma, 3 TB, 2 infusion reactions)
Durez 2007	MTX	RCT	52 weeks	0/14	0/14	0/14
	MP+ MTX	RCT	52 weeks	0/15	0/15	0/15
	IFX + MTX	RCT	52 weeks	1/15 (6.7)	1/15 (6.7)	1/15 (6.7) 1 case of MTX-related pneumonitis
Quinn 2005	PBO + MTX	LTE	104 weeks	0/10	NR	NR
	IFX + MTX	LTE	104 weeks	1/10 (10)	NR	NR 1 cutaneous vasculitis (after single injection; withdrawn)

Table 398: Adverse events and discontinuations due to adverse events: Population 2/3 head to head biologic RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
ATTEST	PBO+MTX	RCT	Day 197	1/110 (0.9)	92/110 (83.6)	13/110 (11.8) (type NR)
	IFX + MTX	RCT	Day 197	8/165 (4.8)	140/165 (84.8)	19/165 (11.5) (type NR)
	ABT + MTX	RCT	Day 197	2/156 (1.3)	129/156 (82.7)	8/156 (5.1) (type NR)
ATTEST	1) PBO+MTX	RCT	Day 365	-	-	-
	2) IFX + MTX	RCT	Day 365	12/165 (7.3)	154/165 (93.3)	30/165 (18.2) (type NR)
	3) ABT + MTX	RCT	Day 365	5/156 (3.2)	139/156 (89.1)	15/156 (9.6) (type NR)
AMPLE	ABT s.c.	RCT	1 year	11/318 (3.5)	280/318 (88.1)	32/318 (10.1) 7 serious infections (3 pneumonia, 2 urinary tract infection, 1 gastroenteritis, 1 helicobacter gastritis), 5 malignancies (2 squamous cell carcinoma of skin, 1 lymphoma, 1 prostate cancer, 1 squamous cell carcinoma of lung), 1 psoriasis, 1 erythema nodosum, 1 leukocytoclastic vasculitis, 2 Raynaud's phenomenon, 1 cutaneous lymphocytic vasculitis, 1 episcleritis, 1 Sjogren's syndrome
	ADA	RCT	1 year	20/328 (6.1)	283/328 (86.3)	30/328 (9.1) 9 serious infections (2 pneumonia, 3 bacterial arthritis, 1 chest wall abscess, 1 diverticulitis, 1 meningitis, 1 staphylococcal bursitis), 4

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						malignancies (2 basal cell carcinoma, 1 small cell lung cancer, 1 transitional cell carcinoma), 1 psoriasis, 1 erythema nodosum, 1 Raynaud's phenomenon, 1 anti-dsDNA seropositivity
REDSEA	ADA + cDMARDs	RCT	12 months	10/60 (16.7)	NR	6/60 (10) There were two deaths, both occurring in patients allocated adalimumab and resulting from ischaemic heart disease, one occurred a week after drug withdrawal other events possibly related to therapy were acute cholecystitis (adalimumab) 1 ovarian cancer
	ETN50+cDMARDs	RCT	12months	12/60 (20)	NR	7/60 (11.6) n=1 diagnosed with heart failure 2 weeks after drug withdrawal: an event believed to be possibly related to the treatment events possibly related to therapy a patient hospitalised with chest

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						symptoms 1 acute myeloid leukaemia group not specified Other serious adverse events included hospitalisation for: a ruptured popliteal cyst; chest symptoms; syncope; suspected femoral fracture; angioedema and urticaria; stillbirth from pregnancy while on treatment, and cellulitis.
ADACTA	TCZ + s.c. PBO	RCT	24 weeks	9/163 (5.5)	133/162 (82.1)	19/162 (12) (including infections, 2 myocardial infarction/acute coronary syndrome, 1 stroke, 1 cancer)
	ADA + i.v. PBO	RCT	24 weeks	10/163 (6.1)	134/162 (82.7)	16/162 (10) (including infections, 2 myocardial infarction/acute coronary syndrome, 1 stroke, 1 cancer, 1 hypersensitivity reaction)

Table 399: Adverse events and discontinuations due to adverse events: Population 2/3 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
AIM Kremer 2006	PBO + MTX	RCT	12 months	1.8	184/219 (84.0)	26/219 (11.9) Related to study drug n=1 (0.5%) Discontinuations due to serious adverse events 3 (1.4) Musculoskeletal and connective tissue disorders 10 (4.6) Infections 5 (2.3) Nervous system disorders 4 (1.8) Cardiac disorders) 2 (0.9) Neoplasms (benign, malignant, and unspecified) 2 (0.9)
	ABT i.v.+ MTX	RCT	12 months	4.2	378/433 (87.3)	65/433(15.0) Related to study drug 15 (3.5) Discontinuations due to serious adverse events 10 (2.3) Musculoskeletal and connective tissue disorders 20 (4.6) Infections 17 (3.9) Nervous system disorders 6 (1.4) Cardiac disorders 4 (0.9)) Neoplasms (benign, malignant, and unspecified) 4 (0.9)
AIM	ABT i.v.+ MTX 2	LTE	2 year	38/593	550/593 (92.6)	149/593 (25.1) “Excluding worsening of arthritis, the most frequent

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
[373]	years or MTX+PBO 1 year then ABTi.v.+ MTX 1 year		s	(6.4)		SAEs were osteoarthritis, pneumonia, basal cell carcinoma, and chest pain, all of which occurred in >0.5% of patients during the cumulative study period”
AIM [374]	ABTi.v.+ MTX 2 years or MTX+PBO 1 year then ABTi.v.+ MTX 1 year	LTE	3 years	n=55	569/593 (96)	NR
ASS	PBO +	RCT	4	0/23	14/23 (60.9)	2/23 (8.7)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
ET	MTX		months			1 atrial fibrillation, 1 study drug overdose
	ABT i.v. + MTX	RCT	4 months	0/27	20/27 (74.1)	0/27
ASSET	ABT i.v. + MTX	LTE	1 year	0/49	41/49 (83.7)	6/49 (12.2) 1 pneumonia, 1 hyperthyroidism and post-operative wound infection (in same patient), 1 study drug overdose and coronary artery disease (in same patient), 1 chronic anaemia, 1 worsening of RA, 1 depression
AUGUST II	PBO + MTX	38 week follow-up of 26 week RCT treatment	38 weeks	2 /76 (2.6)	38/76 (50)	NR
	ADA + MTX	38 week follow-up of 26	38 weeks	2/79 (2.5)	50 /79(63)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
		week RCT treatment				
CHANGE	PBO	RCT	24 weeks	4/87 (4.6)	71/87 (81.6)	8/87 (9.2)
	ADA monotherapy	RCT	24 weeks	12/91(13.2)	90/91 (98.9)	17/91 (18.7) 1 death others not specified
DE019	PBO + MTX	RCT	52 weeks	NR	NR/200 (90.5)	NR 2 malignancies others not specified
	ADA+MTX	RCT	52 weeks	NR	NR	NR
ASSURE	PBO + cDMARDs	RCT	1 year	18/418 (4.3)	360/418 (86.1)	51/418 (12.2) 7 serious infections, 16 neoplasms and the following serious infections: 4 respiratory, 1 dermatologic, 1 urinary, 1 gastrointestinal, 1 gynaecologic, 2

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						opportunistic)
	ABT + cDMARDs	RCT	1 year	43/856 (5.0)	768/856 (89.7)	100/856 (11.7) 22 serious infections, 27 neoplasms and the following serious infections: 9 respiratory, 5 dermatologic, 4 urinary, 2 gastrointestinal)
STAR	PBO + cDMARDs	RCT	24 weeks	8/318 (2.5) (of which 1 considered non-treatment related)	263/318 (82.7)	22/318 (6.9) n=6 serious infections others not specified severe or life-threatening AEs 49/318 (15.4)
	ADA+cDMARDs(	RCT	24 wee	9 /318 (2.8)	275/318 (86.5)	17/318 (5.3) n=4serious infections

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	STAR) n=318		ks			1 death 1 malignancy others not specified severe or life-threatening AEs 38/318 (11.9)
van de Putte 2004	PBO s.c.	RCT	26 weeks	1/110 (0.9)	105/110 (95.5)	16/110 (14.5%)
	ADA mon	RCT	26 weeks	6/113 (5.3)	NR	11.5% (nN NR)
ARMADA	PBO + MTX	RCT	24 weeks	2/62 (3.2)	NR	NR
	ADA+MTX	RCT	24 weeks	0/67	NR	NR
Kim 200	PBO + MTX	RCT	24 wee	NR	82.5% (possibly related to study drug	6/63 (9.5) nr

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
7			ks		28.6%)	
	ADA+MTX	RCT	24 weeks	NR	84.6% (possibly related to study drug 26.2%)	7/65 (10.7) The number of serious AEs (SAEs) reported was comparable between the adalimumab group and the placebo group . Three of the seven SAEs reported in the adalimumab group were of infectious aetiology (2 pneumonia and 1 disseminated tuberculosis), one was a complication due to the SAE of pneumonia (acute respiratory distress syndrome), and the other was vasovagal attack. One death in the adalimumab treatment group
CERTAIN	PBO + cDMARDs	RCT	24 weeks	NR	67.3% (n/N NR)	7.1% Serious infections in 1.0%
	CTZ + DMARDs	RCT	24 weeks	NR	68.8%	5.2% Serious infections in 5.2%
AD	ETN mon	RCT	16	13/15	100/159 (62.9)	8/159 (5.0)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
ORE van Riel 2006			weeks	9 (8.2)		NR “These events represented various organ systems and did not indicate clustering of any single event. None of the serious adverse events were considered to be related to ETN or MTX, with the exception of three events in two patients (one patient from each treatment group). One case of dizziness and one case of blurred vision in the same patient were considered to be related to ETN, although these were not considered by the investigator to be due to demyelinating disease. One case of dyspnoea was considered to be related to ETN plus MTX treatment.”
ADORE	ETN+MTX	RCT	16 weeks	9/155 (5.8)	109/155 (70.3)	7/155 (4.5)
CREATE IIb	DMARD +PBO n=65	RCT	24 weeks	9.2%	NR	NR
	ETN50 +	RCT	24	3.1%	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
Keystone 2012	DMARD n=64		weeks			
ETN309	SSZ+PBO	RCT	24 weeks	due to SAE 1/50	NR non-infectious AEs 29/50 (58)	NR non-infectious SAEs 1/50 (2%)
	ETN + PBO	RCT	24 weeks	due to SAE 1/103	NR non-infectious AEs 74/103 (71.8)	NR non-infectious SAEs 3/103 (2.9)
	ETN + SSZ	RCT	24 weeks	due to SAE 1/101	nr non-infectious AEs 72/101 (71.3)	NR non-infectious SAEs 5/101 (5)
ETN309 Co	SSZ+PBO	RCT	2 years	NR	NR non-infectious AEs TEAE 32/50 (64)	2/50 (4) “There was no clustering of SAE. In the 2 years of the study, 23 patients receiving the combination, 27 receiving etanercept

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
mbe 2009						and two receiving sulfasalazine had one or more SAE. Non-infectious SAE were significantly greater in patients receiving etanercept (20.8% for the combination and 20.4% for etanercept alone) compared with 4% for patients receiving sulfasalazine..”
	ETN + PBO	RCT	2 years	NR	NR non-infectious AEs 90 /103 (87.4)	27/103 (26.2)
	ETN + SSZ	RCT	2 years	NR	NR non-infectious AEs 80/101 (79.2)	23/101 (22.8)
JESMR	ETN monotherapy	RCT	52 weeks	4/71 (5.6)	NR	2/71 (2.8) 2 bone fractures
	ETN + MTX	RCT	52 weeks	1/76 (13.1)	NR	7/76 (9.2) 3 bone fractures, 1 congestive heart failure, 1 cellulitis (in same patient as one of the fractures), 1 herpes zoster, 1 brain haemorrhage, 1 mammary carcinoma

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
Lan 2004	PBO+MTX	RCT	12 weeks	1/29 (3.4)	NR	NR 1 bronchiolitis obliterans
	ETN+MTX	RCT	12 weeks	1/29 (3.4)	NR Most frequently occurring AEs in line with SPC	NR 1 viral pneumonia
LARA	MTX + DMARD	RCT	24 weeks	NR	97/142 (68.3)	2/142 (1.4) NR
	ETN50+ MTX	RCT	24 weeks	NR	193/281 (68.7)	10/281 (3.6) NR
RACAT	MTX + SSZ + HCQ on treatment analysis n=222	RCT including cross-over	48 weeks	12/222 (5.4)	170/222 (76.6)	25/222 (11.3) some patients counted in more than one event, n= Cardiac disorders 4 Gastrointestinal disorders 5 Infections and infestations 4 Renal and urinary disorders 1 Respiratory, thoracic and mediastinal disorders 4

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	(some patients exposed to both treatments throughout trial)					Surgical and medical procedures 3 Vascular disorders 3 Other (events occurring fewer than 3 times) 9
	ETN50 + MTX on treatment analysis n=219 (some patients exposed to both treatments throughou	RCT including cross-over	48 weeks	5/219 (2.3)	165/219 (75.3)	26/219 (11.9) some patients counted in more than one event, n= Cardiac disorders 1 Gastrointestinal disorders 4 Infections and infestations 12 Renal and urinary disorders 3 Respiratory, thoracic and mediastinal disorders 1 Surgical and medical procedures 5 Vascular disorders 4 Other (events occurring fewer than 3 times) 9

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	t trial)					
Weinblatt 1999	PBO + MTX	RCT	24 weeks	1/30 (3.3)	NR	NR
	ETN + MTX	RCT	24 weeks	2/59 (3.4)	NR	NR
APPEAL	MTX + DMARD (SSZ, HCQ or LEF)	RCT	16 weeks	8/103 (7.8)	79/103 (77)	3/103 (3) 1 infection/infestation, 2 increased alanine aminotransferase
	ETN + MTX	RCT	16 weeks	3/197 (1.5)	134/197 (68)	6/197 (3) 1 cardiac disorder, 1 gastrointestinal disorder, 1 general disorder, 3 infections and infestations, 2 poisoning and procedural complications
GO-FORT	PBO + MTX	RCT	24 weeks	NR	67/88 (76.1)	1/88 (1.1) 1 intervertebral disc protrusion

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
H	GOL + MTX	RCT	24 weeks	NR	70/86 (81.4)	2/86 (2.3) 1 ileus, 1 bone neoplasm (borderline or low malignancy potential)
GO-FORWARD	PBO + MTX	RCT	24 weeks	5/133 (3.8)	89/134 (66.4)	5/134 (3.7) (type NR)
	GOL + MTX	RCT	24 weeks	2/89 (2.3)	87/212 (41.0)	9/212 (4.2) (type NR)
GO-FORWARD [82]	PBO + MTX	RCT	52 weeks	8/133 (6.0)	98/133 (73.7)	6/133 (4.5) (type NR)
	GOL + MTX	RCT	52 weeks	7/212 (3.3)	167/212 (78.8)	17/212 (8.0) (type NR)
Kay 2008	IFX + MTX (PBO group	RCT	52 weeks	3/25 (12.0)	16/25 (64.0)	3/25 (12.0) (type NR)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	crossed over to IFX at week 20)					
	GOL + MTX		52 weeks	4/37 (10.8)	34/37 (91.9)	7/37 (18.9) (type NR)
Abe 2006	PBO + MTX	RCT	14 weeks	1/47 (2.1)	NR	1/47 (2.1) (type NR for extracted arm)
	IFX + MTX	RCT	14 weeks	1/49 (2.0)	NR	0
Abe 2006	PBO group crossover to IFX	LTE	To week 36 of LTE	9/41 (22.0)	NR	6/41 (14.6) (type NR for extracted arm)
	IFX +	LTE	To	4/49	NR	2/49 (4.1) (type NR for extracted arm)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	MTX		week 36 of LTE	(8.2)		
ATTRACT [139]	PBO + MTX	RCT	54 weeks	7/88 (8.0)	94%	18/86 (21) (type NR)
	IFX + MTX	RCT	54 weeks	5/86 (5.8)	NR	10/88 (11) (type NR)
ATTRACT [375]	PBO + MTX	LTE	102 weeks	NR	NR	28/NR(33) (type NR)
	IFX + MTX	LTE	102 weeks	NR	NR	29/NR (33) (type NR)
START	PBO + MTX	RCT	22 weeks	5/361 (1.4)	239/361 (66.2)	27/361 (7.5) 1 fever, 1 osteoarthritis, 4 rheumatoid arthritis

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
	IFX + MTX	RCT	22 weeks	0/360	251/360 (69.7)	28/360 (7.8) 2 pneumonia, 1 cellulitis, 1 chest pain, 2 osteoarthritis, 1 cardiac failure, 1 myocardial infarction, 2 uterine fibroid, 1 rheumatoid arthritis
START	IFX + MTX	LTE	54 weeks	NR	211/244 (86.5)	39/244 (16.0) 5 pneumonia1 active TB, 1 abscess, 2 pyelonephritis
Swefot	SSZ + HCQ + MTX	RCT	24 months	22/130 (17.0)	NR/130 (45)	SAEs=1 (1) (generalised symptoms)
	IFX + MTX	RCT	24 months	19/128 (14.8)	NR/128 (38)	SAEs=2 (2) (persistent fever and generalised symptoms)
Zhang 2006	PBO + MTX	RCT	18 weeks	4/86 (4.7)	48/86 (55.8)	NR
	IFX + MTX	RCT	18 weeks	6/87 (6.9)	57/87 (65.5)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
ACT-RAY [146]	TCZ + oral PBO	RCT	52 weeks	NR	228/276 (82.6)	26/276 (9.4)
	TCZ + MTX	RCT	52 weeks	NR	NR/277 (81.9)	24/277 (8.7)
Nishimoto 2004	PBO i.v.	RCT	12 weeks	4/53 (7.5)	NR/53 (56)	2/53 (3.8) (type NR)
	TCZ	RCT	12 weeks	2/55 (3.6)	NR/55 (51)	NR for TCZ 8 mg/kg
STREAM (LTE of Nishimot	PBO i.v.	LTE	To year 5	-	-	-
	TCZ	LTE	To year 5	32/143 (22.4)	NR	77/143 (53.8) (including joint surgery N=20 (most common), pneumonia N=9, herpes zoster N=7, tendon rupture N=5, humerus fracture N=4, acute bronchitis N=2)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
o 2004) [376]						
SAMURAI	cDMARDs	RCT	52 weeks	5/145 (3.5)	NR/145 (82)	NR/145 (13) only serious infections listed, not other SAEs 8 serious infections were reported: 3 (2.1%) patients with gastroenteritis, 2 (1.4%) with pneumonia, and 1 (0.7%) each with upper respiratory tract infection, herpes zoster and sepsis
	TCZ	RCT	52 weeks	17/157 (10.8)	NR/157 (89)	NR/157 (18) only serious infections listed, not other SAEs 12 serious infections were reported: 3 (1.9%) patients with pneumonia, 2 (1.3%) with upper respiratory tract infection, 2 (1.3%) with cellulitis, 1 (0.6%) each with gastroenteritis, herpes zoster, herpes simplex, perianal abscess

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
						and an unidentified infection
SATORI	PBO i.v. + MTX	RCT	24 weeks	3/64 (4.7)	46/64 (71.9) (104 AEs)	3/64 (4.7) (1 pneumonia, 1 spinal compression fracture, 1 femoral neck fracture)
	TCZ + PBO capsules	RCT	24 weeks	2/61 (3.3)	56/61 (91.8%) (211 AEs)	4/61 (6.6) (1 pneumonia, 1 infectious arthritis, 1 colonic polyp, 1 headache)
TOWARD	PBO + stable cDMARDs	RCT	24 weeks	8/414 (1.9)	253/414 (61.1)	18/414 (4.3) (related SAE=6 (1.4) type NR)
	TCZ + stable DMARDs	RCT	24 weeks	31/802 (3.9)	584/802 (72.8)	54/802 (6.7) (related SAE=23 (2.9) type NR)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Discontinuation due to adverse event(s), nN (%)	Number of patients experiencing 1 or more adverse event, nN, (%)	Number of patients experiencing 1 or more serious adverse event, nN (%)
			[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 400: Specific categories of adverse events: Population 1 RCTs of biologic interventions vs. DMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection (nN) (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	RCT	52 weeks	NR	1/32 (3)	NR	0	NR	NA
	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28	RCT	52 weeks	NR	2/33 (6)	NR	2/33 (6)	NR	NA

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection (nN) (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
HIT HARD[84]	MTX + PBO for 24 weeks followed by OL MTX for 24 weeks	LTE	48 weeks	10/85 (11.8)	4/85 (4.7)	NR	3/85 (3.5)	4/85 (4.7)	NR
	ADA + MTX for 24 weeks followed by OL MTX for 24 weeks	LTE	48 weeks	16/87 (18.4)	3/87 (3.4)	NR	0/87	14/87 (16.1)	NR
OPERA [97]	PBO + MTX + steroid	RCT	12 months	NR	3/91 (3.3)	NR	2/91 (2.2)	NR	NR
	ADA + MTX + steroid	RCT	12 months	NR	3/89 (3.4)	NR	3/89 (3.4)	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection (nN) (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
PREMIER	ADA (all patients who received ≥ 1 dose)	LTE	5 years	NR	3.3 events per 100 patient-years (nN NR)	NR	11/497 (2.2)	NR	NR
COMET	PBO + MTX	RCT period 1, 52 weeks	52 weeks	8/268 (3.0)	NR	NR	4/268 (1.5)	NR	NR
	ETN+MTX	RCT period 1, 52 weeks	52 weeks	5/274 (1.8)	NR	NR	4/274 (1.5)	NR	NR
COMET [135]	MTX in year 1 MTX	RCT period 2	Weeks 52-104	NR	2/99 (2.0%)	NR	3/99 (3.0%)	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection (nN) (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
	in year 2								
COMET	MTX year 1 ETN+MTX in year 2	RCT period 2	Weeks 52-104	NR	1/90 (1.1)	NR	5/90 (5.6)	NR	NR
COMET	ETN+MTX in year 1 ETN+MTX in year 2	RCT period 2	Weeks 52-104	NR	1/111 (0.9)	NR	0 (0)	NR	NR
COMET	ETN+MTX in year 1 ETN in year 2	RCT period 2	Weeks 52-104	NR	2/111 (1.8)	NR	1/111 (0.9)	NR	NR
ERA	PBO + MTX	RCT	12 months	NR	NR	<3%	2/217 (0.9)	16/217 (7.4)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection (nN) (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
	ETN + PBO	RCT	12 months	NR	NR	<3%	3/207 (1.4)	77/207 (37.2)	NR
ERA	PBO + MTX	LTE	2 years	NR	9/217 (4.1)	NR	3/217 (1.4)	19/217 (8.8)	NR
	ETN + PBO	LTE	2 years	NR	7/207 (3.4)	NR	4/207 (1.9)	81/207 (39.1)	NR
GO-BEFORE	PBO + MTX	RCT	24 weeks	52/160 (32.5)	3/160 (1.9)	NR	2/160 (1.3)	3/160 (1.9)	NA
	GOL + MTX	RCT	24 weeks	54/158 (34.2)	2/158 (1.3)	NR	1/158 (0.6)	7/158 (4.4)	NA
GO-BEFORE [136]	PBO + MTX	LTE	Week 104	NR	NR	NR	2 (no N provided, assumed N=160)	NR	NR
	GOL + MTX	LTE	Week 104	NR	5.5%	NR	6 (no N provided, assumed N=158)	NR	NR
ASPIRE	PBO i.v. +	RCT	54 weeks	NR	21/372 (5.6)	NR	0	N/A	20/291 (6.9)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection (nN) (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
	MTX								
	IFX + MTX	RCT	54 weeks	NR	6/291 (2.1) [a]	NR	0	N/A	79/372 (21.2) (2 classed as serious)
Durez 2007	MTX	RCT	52 weeks	14/14 (100)	0/14	NR	NR	NR	NR
	MTX + MP	RCT	52 weeks	12/15 (80)	0/15	NR	NR	NR	NR
	IFX + MTX	RCT	52 weeks	12/15 (80)	1/15 (6.7)	NR	NR	NR	NR
Quinn 2005	PBO + MTX	LTE	104 weeks	NR	NR	NR	NR	NR	0/10
	IFX + MTX	LTE	104 weeks	NR	NR	NR	NR	NR	1/10 (10%)

Table 401: **Specific categories of adverse events: Population 2/3 head to head biologic RCTs**

Trial name / Author, year	Treatment arms for which data extraction performed	RCT / LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) n/N (%)
ATTEST[66]	PBO+MTX	RCT	Day 197	NR	3/110 (2.7)	NR	1/110 (0.9)	N/A	10.0%
	IFX + MTX	RCT	Day 197	NR	7/165 (4.2)	NR	2/165 (1.2)	N/A	18.2%
	ABT + MTX	RCT	Day 197	NR	2/156 (1.3)	NR	1/156 (0.6)	N/A	5.1%
ATTEST[66]	PBO+MTX	RCT	Day 365	-	-	-	-	-	-
	IFX + MTX	RCT	Day 365	NR	14/165 (8.5)	NR	2/165 (1.2)	N/A	41/165 (24.8)
	ABT + MTX	RCT	Day 365	NR	3/156 (1.9)	NR	1/156 (0.6)	N/A	11/156 (7.1)
AMPLE	ABT s.c.	RCT	2 years	63.2%	7/318 (2.2)	NR	5/318 (1.6)	12/318 (3.8)	NA
	ADA	RCT	2 years	61.3%	9/328 (2.7)	NR	4/328 (1.2)	30/328 (9.1)	NA
REDSEA	ADA + cDMARDs	RCT	12 months	NR	NR	NR	1/60 (1.7)	9/60 (15)	NA
	ETN50+cDMARDs	RCT	12 months	NR	NR	NR	1/60 (1.7)	19/60 (31.7)	NA
ADACTA[55]	TCZ + s.c. PBO	RCT	24 weeks	77/162 (47.5)	5/162 (3.1)	NR	1/162	NA	NR
	ADA + i.v. PBO	RCT	24 weeks	68/162 (42.0)	5/162 (3.1)	NR	1/162	NR	NA

Trial name / Author, year	Treatment arms for which data extraction performed	RCT / LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) n/N (%)
ADACTA[55]	TCZ	LTE	To year 5	NR	25/143 (17.5) (pneumonia, herpes zoster, acute bronchitis, pyelonephritis)	NR	4/143 (2.8) (bladder cancer, breast cancer, large intestine carcinoma, intraductal papilloma).	NA	NR

Table 402: **Specific categories of adverse events: Population 2/3 RCTs of biologic interventions vs. DMARD(s) or PBO**

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
AIM Kremer 2006	PBO + MTX	RCT	12 months	NR	5/219 (2.3)	NR	NR	NR	Acute infusional adverse events 37/219 (16.9)
	ABT i.v.+ MTX	RCT	12 months	NR	17/433 (3.9)	NR	NR	NR	Acute infusional adverse events 38/433(8.8)
AIM Kremer 2008 [373]	ABT i.v.+ MTX 2 years or MTX + PBO 1 year then ABT i.v.+ MTX 1 year	LTE	2 years	400/593 (67.5)	43/593 (7.3)	NR	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
ASSET	PBO + MTX	RCT	4 months	6/23 (26.1)	0/23	NR	0/23	NA	Acute infusion events: 4/23 (17.4) Peri-infusional events: 5/23 (21.7)
	ABT i.v. + MTX	RCT	4 months	10/27 (37.0)	0/27	NR	0/27	NA	Acute infusion events: 0/27 Peri-infusional events: 4/27 (14.8)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
ASSET	ABT i.v. + MTX (OLE)	LTE	1 year	26/49 (53.1)	1/49 (2.0)	NR	0/49	NA	Acute infusion events: 2/49 (4.1) Peri-infusional events: 6/49 (12.2)
ASSURE	PBO + cDMARDs	RCT	1 year	224/418 (53.6)	7/418 (1.7)	NR	NR	NR	NR
	ABT + cDMARDs	RCT	1 year	470/856 (54.9)	22/856 (2.6)	NR	NR	NR	NR
AUGUST II	PBO + MTX	38 week follow-up of 26 week RCT treatment	38 weeks	NR	1/76 (1.3)	NR	NR	NR	NA
	ADA + MTX	38 week follow-up of 26 week RCT	38 weeks	NR	3/79 (3.8)	NR	NR	NR	NA

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
		treatment							
CHANGE	PBO	RCT	24 weeks	32/87 (36.8)	1/87 (1.1)	NR	2/87 (2.3)	2/87 (2.3)	NR
	ADA monotherapy	RCT	24 weeks	41/91 (45.1)	6/91 (6.6)	NR	0	28/91 (30.8)	NR
DE019	PBO + MTX	RCT	52 weeks	Upper respiratory tract infection 13.5% Infection 4.5%	NR	NR	0	n/200 (24%)	NR
	ADA + MTX	RCT	52 weeks	Upper respiratory tract	NR	NR	Across both ADA groups,	n/207 (26%)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
				infection 19.8% Infection 7.2%			Four adalimumab-treated patients developed non-skin cancers, including non-Hodgkin's lymphoma, adenocarcinoma, testicular seminoma, and breast cancer (not stated which		

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
							ADA group)		
STAR	PBO + cDMARDs	RCT	24 weeks	157/318 (49.4)	6/318 (1.9)	NR	0	37 (11.6%)	NA
	ADA + cDMARDs	RCT	24 weeks	166 (52.2%)	4 (1.3%)	NR	1/318 (0.3)	62 (19.5%) [a]	NA
van de Putte 2004	PBO s.c.	RCT	26 weeks	NR	NR	NR	1/110 (0.9)	1/110 (0.9)	NA
	ADA monotherapy	RCT	26 weeks	NR	NR	NR	4/434 (0.9) (of all 4 ADA groups)	11/113 (9.7)	NA
ARMADA	PBO + MTX (n=62)	RCT	24 weeks	any infection NR upper respiratory tract	NR	NR	NR	pain 3.2% reaction 0%	NA

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
				infection 9.7%					
	ADA + MTX (n=67)	RCT	24 weeks	any infection NR upper respiratory tract infection 14.9%	NR	NR	NR	pain 10.4% reaction 1.5%	NA
Kim 2007	PBO + MTX	RCT	24 weeks	n/63 (34.9)	NR	NR	0	NR	NR
	ADA + MTX	RCT	24 weeks	n/65 (36.9)	NR	NR	0	NR	NR
CERTAIN	PBO + cDMARDs	RCT	24 weeks	NR	(n/N NR) 1.0%	NR	NR	NR	NR
	CTZ + DMARDs	RCT	24 weeks	NR	(n/N NR) 2.1%	NR	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
ADORE van Riel 2006	ETN monotherapy	RCT	16 weeks	39/159 (24.5)	2/159 (1.3)	NR	NR	NR	NR
	ETN + MTX	RCT	16 weeks	50/155 (32.3)	1/155 (0.7)	NR	NR	NR	NR
CREATE IIb Keystone 2012	PBO + DMARD	RCT	24 weeks	NR	0/65	NR	NR	NR	NR
	ETN50 + DMARD	RCT	24 weeks	NR	0/64	NR	NR	NR	NR
ETN309	SSZ + PBO	RCT	24 weeks	13/50 (26)	0	NR	0	1/50 (2)	NR
	ETN + PBO	RCT	24 weeks	47/103 (45.6) [a] vs. SSZ	2/103 (1.9)	NR	2/103 (1.9)	33/103 (32.0) a vs. SSZ	NR
	ETN + SSZ	RCT	24 weeks	31/101 (30.7) a vs. SSZ, a vs.	0	NR	0	16/101 (15.8) [a] vs. SSZ a vs. ETN+PBO	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
				ETN+PBO					
ETN309 [Combe 2009]	SSZ + PBO	RCT	2 years	21/50 (42.0)	NR	NR	NR	2/50 (4.0)	NR
	ETN + PBO	RCT	2 years	76/103 (73.8) a vs. SSZ	NR	NR	NR	34/103 (33.0) a vs. SSZ	NR
	ETN + SSZ	RCT	2 years	60/101 (59.4) a vs. ETN+PBO	NR	NR	NR	21/101(20.8) a vs. SSZ	NR
JESMR	ETN monotherapy	RCT	52 weeks	19/71 (26.8)	0/71	NR	NR	13/71 (18.3)	NR
	ETN + MTX	RCT	52 weeks	21/76 (27.6)	2/76 (2.6)	NR	NR	7/76 (9.2)	NR
Lan 2004	PBO + MTX	RCT	12 weeks	NR	NR	NR	NR	0/29	NR
	ETN + MTX	RCT	12 weeks	NR	NR	NR	NR	1/29 (3.5)	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
LARA	MTX + DMARD	RCT	24 weeks	31/142 (21.8)	0	NR	NR	NR	NR
	ETN50 + MTX	RCT	24 weeks	107/281 (38.1%) [a]	5/281 (1.8)	NR	NR	NR	NR
Moreland 1999 Mathias 2000 data from Moreland 1999	PBO	RCT	6 months	NR	NR	NR	NR	n/80 (13)	NR
	ETN+PBO	RCT	6 months	NR	NR	NR	NR	n/78 (49) [b]	NR
RACAT	MTX + SSZ + HCQ on treatment analysis n=222 (some patients	RCT including cross-over	48 weeks	56/222 (25.2)	4/222 (1.8)	NR	NR	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
	exposed to both treatments throughout trial)								
	ETN50 + MTX on treatment analysis n=219 (some patients exposed to both treatments throughout trial)	RCT including cross-over	48 weeks	82/219 (37.4)	9/219 (4.1)	NR	NR	NR	NR
Wajdula 2000 [358]	PBO	RCT	12 weeks	NR	NR	NR	1/105 (1.0)	NR	NR
	ETN	RCT	12 weeks	NR	NR	NR	0/111	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
Weinblatt 1999	PBO + MTX,	RCT	24 weeks	n/30 (63)	NR	NR	NR	n/30 (7)	NR
	ETN + MTX	RCT	24 weeks	n/59 (51)	NR	NR	NR	n/59 (42)	NR
Kremer 2003 (LTE of Weinblatt 1999) [115]	ETN + MTX or MTX + PBO followed by ETN + MTX n=79	LTE	3 year LTE	NR	4/79 (5.1) required hospitalisation	NR	3/79 (3.8)	NR	NR
GO-FORTH	PBO + MTX	RCT	24 weeks	39/88 (44.3)	0/88	NR	0/88	7/88 (8.0)	NA
	GOL + MTX	RCT	24 weeks	36/86 (41.9)	0/86	NR	0/86	8/86 (9.3)	NA
GO-FORWA	PBO + MTX	RCT	24 weeks	37/134 (27.6)	1/134 (0.7)	NR	1/134 (0.7) (basal cell	4/134 (3.0)	NA

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
RD					(UTI)		cancer)		
	GOL + MTX	RCT	24 weeks	34/212 (16.0)	2/212 (0.9) (1 cellulitis, 1 s.c. abscess)	NR	0	5/212 (2.4)	NA
GO-FORWARD	PBO + MTX	RCT	52 weeks	42/133 (31.6)	1/133 (0.8)	NR	2/133 (1.5)	4/133 (3.0)	NA
	GOL + MTX	RCT	52 weeks	98/212 (46.2)	4/212 (1.9)	NR	3/212 (1.4)	10/212 (4.7)	NA

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
Kay 2008	IFX + MTX (PBO group crossed over to IFX at week 20	RCT	52 weeks	9/25 (36.0)	1/25 (4.0)	NR	0/25	NA	NR
	GOL + MTX	RCT	52 weeks	23/37 (62.2)	1/37 (2.7)	NR	1/37 (2.7)	6/37 (16.2)	NA
Abe 2006	PBO + MTX	RCT	14 weeks	17/47 (36.2)	NR Pneumonia = 0	NR	NR	N/A	17/47 (36.2)
	IFX + MTX	RCT	14 weeks	22/49 (44.9)	NR Pneumonia = 1 (2.0)	NR	NR	N/A	23/49 (46.9)
Abe 2006	PBO group crossover to IFX	LTE	To week 36 of LTE	22/41 (53.7)	NR	NR	NR	N/A	17/41 (41.5)
	IFX + MTX	LTE	To week	31/49	NR	NR	NR	N/A	33/49 (67.3)

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
			36 of LTE	(63.3)					
ATTRACT Lipsky *et al.*, 2000 [139]	PBO i.v. + MTX	RCT	54 weeks	NR	7/86 (8.1)	35%	0	NA	(Serious infusion reactions) 0
	IFX + MTX	RCT	54 weeks	NR	2/88 (2.3)	NR	0	NA	0
ATTRACT Maini *et al.*, 2004 [375]	PBO i.v. + MTX	LTE	102 weeks	NR	11/NR (13)	NR	1/NR (1)	NA	Serious infusion reactions = 0
	IFX + MTX	LTE	102 weeks	NR	10/NR (11)	NR	1/NR (1)	NA	Serious infusion reactions = 0
Durez	MP + MTX	RCT	14	NR	0/NR	NR	NR	N/A	0/NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
2004			weeks (N unclear)						
	IFX + MTX		14 weeks (N unclear)	NR	0/NR	NR	NR	N/A	0/NR
START	PBO + MTX	RCT	22 weeks	38/361 (10.5) (upper respiratory tract infection)	6/361 (1.7)		0/361		Serious infusion reactions: 1/361 (0.3)
	IFX + MTX	RCT	22 weeks	35/360 (9.7) (upper respiratory tract infection)	6/360 (1.7)		2/360 (0.6)		Serious infusion reactions: 0/360
START	IFX + MTX (not dose escalated)	LTE	54 weeks	119/244 (49%)	11/244 (4.5)		1/244 (0.4)		Serious infusion reactions: 2/244 (0.8)
Swefot	SSZ + HCQ +	RCT	24	AEs=1/13	NR	NR	AEs=0	NR	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
	MTX		months	0 (1)					
	IFX + MTX	RCT	24 months	AEs=8/128 (6)	NR	NR	AEs=1 /128 (1)	NR	NR
ACT-RAY [146]	TCZ + oral PBO	RCT	52 weeks	NR	9/276 (3.3)	NR	NR	NA	NR
	TCZ + MTX	RCT	52 weeks	NR	10/277 (3.6)	NR	NR	NA	NR
Nishimoto 2004	PBO	RCT	12 weeks	NR	NR	NR	NR	NA	15%
	TCZ	RCT	12 weeks	NR	NR	NR	NR	NA	16%
STREAM [376](LTE of Nishimoto 2004)	PBO	LTE	To year 5	-	-	-	-	-	-
	TCZ	LTE	To year 5	NR	25/143 (17.5)	NR	4/143 (2.8) (bladder cancer, breast cancer,	NA	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
							large intestine carcinoma, intraductal papilloma).		
SAMURAI	cDMARDs	RCT	52 weeks	NR	8/145 (5.5)	NR	0/145	NR	NA
	TCZ	RCT	52 weeks	NR	12/157 (7.6)	NR	3/157 (1.9)	NR	11/157 (7.0)
SATORI	PBO + MTX	RCT	24 weeks	NR	NR	NR	NR	NA	NR
	TCZ + PBO capsules	RCT	24 weeks	NR	NR	NR	NR	NA	7/61 (11.5)
TOWARD	PBO i.v. + stable cDMARDs	RCT	24 weeks	131/414 (31.6)	8/414 (1.9)	NR	NR	NA	NR

Trial name / Author, year	Treatment arms for which data extraction performed	RCT/ LTE phase	Assessment time point	Number of patients experiencing 1 or more infection nN (%)	Number of patients experiencing 1 or more serious infection nN, (%)	Number of patients experiencing any infection requiring antibiotics nN (%)	Number of patients experiencing 1 or more malignancy nN (%)	Number of patients experiencing 1 or more injection-site reaction (s.c. administration) nN (%)	Number of patients experiencing 1 or more infusion-related reaction (i.v. administration) nN (%)
	TCZ + stable DMARDs	RCT	24 weeks	300/802 (37.4)	22/802 (2.7)	NR	NR	NA	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 403: Number of deaths: Population 1 RCTs biologic vs. cDMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Deaths (nN)	Cause of death	Considered by investigators/adjudicators to be related to study drug?
GUEPARD[83]	Initial MTX 12 weeks, then step-up therapy in both groups based on DAS28	1 year	0/32	NA	NA
	Initial ADA+MTX 12 weeks, then step-up therapy in both groups based on DAS28RACAT	1 year	0/33	NA	NA
HIT HARD	MTX + PBO for 24 weeks followed by OL MTX for 24 weeks	48 weeks	0/85	NA	NA
	ADA + MTX for 24 weeks followed by OL MTX for 24 weeks	48 weeks	0/87	NA	NA
OPERA [97]	MTX + PBO + steroid	12 months	1/91 (1.1%)	Pneumonia 4 months after terminating the study	NR
	ADA + MTX + steroid	12 months	0/89	NA	NA
PREMIER	MTX + PBO	2 years	1/257 (0.4%)	Pneumonia	NR
	ADA mon + PBO	2 years	4/274 (1.5%)	1 COPD/pulmonary disease and pulmonary hypertension sudden death; 1 metastatic liver cancer (unknown primary); 1 metastatic	NR

				colon cancer; 1 liver failure (pre-existing cirrhosis)	
	ADA + MTX	2 years	1/268 (0.4%)	Ovarian cancer	NR
PREMIER	MTX + PBO to OL ADA mon	5 years LTE	0.6% (n/N NR)	NR	NR
	ADA mon + PBO to OL ADA mon	5 years LTE	0.6% (n/N NR)	NR	NR
	ADA + MTX to OL ADA mon	5 years LTE	1.1% (n/N NR)	NR	NR
COMET RefID24641 Emery 2010	MTX in year 1 MTX in year 2	2 years	1/99	Pneumonia and adenocarcinoma of the lungs with metastasis	NR
	MTX year 1 ETN+MTX in year 2	2 years	0	NA	NA
	ETN+MTX in year 1 ETN+MTX in year 2	2 years	0	NA	NA
	ETN+MTX in year 1 ETN in year 2	2 years	1/111	Pneumonia	NR
ERA	MTX + PBO	12 months	0/217	NA	NA

			(0%)		
	ETN + PBO	12 months	1/207 (0.5%)	Non-infectious complications resulting from dissection of a pre-existing aortic aneurysm	NR
ERA	MTX + PBO	2 years	0/217 (0%)	NA	NA
	ETN + PBO	2 years	1/207 (0.5%)	See above	NA
GO-BEFORE	PBO + MTX	RCT 24 weeks	0	NA	NA
	GOL + MTX	RCT 24 weeks	1	Suicide	NR
GO-BEFORE [136]	PBO + MTX	LTE 104 weeks	0	NA	NA
	GOL + MTX	LTE 104 weeks	4/159 (2.5%)	1 hypoglycaemic coma, 1 lung cancer, 1 septic shock, 1 probable non-small cell lung cancer	NR
ASPIRE	PBO i.v. + MTX	RCT 54 weeks	2	1 due to respiratory failure attributed to MTX-related drug toxicity, 1 due to upper gastrointestinal bleed	NR
	IFX + MTX	RCT 54 weeks	1	Cardiac arrest	NR
Durez 2007	MTX	52 weeks	0/14	NA	NA
	MTX + MP	52 weeks	0/15	NA	NA
	IFX + MTX	52 weeks	0/15	NA	NA

Table 404: Number of deaths: Population 2/3 head to head biologic RCTs

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Deaths (nN)	Cause of death	Considered by investigators/adjudicators to be related to study drug?
ATTEST[66]	PBO+MTX	RCT day 197	0	NA	NA
	IFX + MTX	RCT day 197	1/165	Cerebrovascular accident	NR
	ABT + MTX	RCT day 197	1/ 156	Fibrosarcoma	NR
ATTEST[66]	PBO+MTX	RCT day 365	No further deaths	NA	NA
	IFX + MTX	RCT day 365	1 additional death	Patient with peritoneal TB, death due to septic shock following surgery	NR
	ABT + MTX	RCT day 365	No further deaths	NA	NA
AMPLE	ABT s.c.	1 year	1/318	Sudden cardiac arrest	No
	ADA	1 year	0/328	NA	NA
REDSEA	ADA + cDMARDs	12 months	2/60	Both ischaemic heart disease	NR
	ETN50 + cDMARDs	12 months	0/60	NA	NA
ADACTA[55]	TCZ + oral PBO	24 weeks	2/162	1 sudden death, 1 illicit drug overdose	Overdose considered by study team unrelated to study drug. Sudden death considered by study team to be possibly related to study drug (unautopsied).
	ADA + i.v. PBO	24 weeks	0	NA	NA

Table 405: Number of deaths: Population 2/3 RCTs biologic vs. cDMARD(s) or PBO

Trial name / Author, year	Treatment arms for which data extraction performed	Assessment time point	Deaths (nN)	Cause of death	Considered by investigators/adjudicators to be related to study drug?
AIM Kremer 2006	MTX + PBO	12 months	1/219	Pneumonia, sepsis, and multiorgan failure.	NR
	ABT i.v .+ MTX	12 months	1/433	History of tuberculosis, asbestos exposure, and pulmonary fibrosis, died of bronchopneumonia, pulmonary aspergillosis, and septicemia	NR
AIM Kremer 2013 RefID24721	ABT i.v.+ MTX 2 years or MTX+PBO 1 year then ABT i.v.+ MTX 1 year	LTE 3 years	9/593 during LTE	Myocardial ischaemia with postprocedural complications, lobar pneumonia, lung cancer, pneumonia/sepsis, malignant melanoma, aortic aneurysm, 3 cases of cardiac arrest.	NR
ASSET	PBO + MTX	4 months	0/23	NA	NA
	ABT i.v.+ MTX	4 months	0/27	NA	NA
ASSET	ABT i.v.+ MTX	1 year LTE	0/49	NA	NA
ASSURE	PBO + cDMARDs	1 year	4/418 (1.0%)	Congestive heart failure, cardiopulmonary arrest, cardiac arrest, pneumonia	Three no, one possibly

	ABT + cDMARDs	1 year	5/856 (0.6%)	Hypertensive heart disease, coronary atherosclerosis/acute ischaemic cardiopathy, central atherosclerosis/advanced coronary atherosclerosis with focal stenosis, cardiac arrest	Four no, one can't tell (unautopsied)
AUGUST II	MTX+PBO	38 week follow-up of 26week RCT treatment	0/76	NA	NA
	ADA+MTX	38 week follow-up of 26week RCT treatment	0/79	NA	NA
CHANGE	PBO	24 weeks	0/87	NA	NA
	ADA mon	24 weeks	1/91 (1.1%)	Interstitial lung disease and lung infection	Considered possibly related to treatment
DE019	MTX+PBO	52 weeks	0/200	NA	NA
	ADA+MTX	52 weeks	2/207	1 related to multiple fractures and 1 related to urosepsis	NR
STAR	PBO + cDMARDs	24 weeks	0/318	NA	NA
	ADA + cDMARDs	24 weeks	1/318 (0.3%)	Secondary streptococcal A superinfection	NR
van de Putte 2004	PBO s.c.	26 weeks	1	Complications of bowel obstruction	All stated by authors to be unrelated or unlikely to be related to study drug.
	ADA mon	26 weeks	3 in ADA group (dose not specified)	Metastatic adenocarcinoma, cholangiocarcinoma, and myocardial infarction	

ARMADA	MTX + PBO	24 weeks	0/62	NA	NA
	ADA + MTX	24 weeks	0/67	NA	NA
ARMADA [377]	ADA + MTX	4 years LTE	6/262	congestive heart failure, acute myocardial insufficiency, aortic aneurysm previously treated surgically, cerebrovascular accident, intracranial haemorrhage, acute kidney failure	NR
Kim 2007	MTX+PBO	24weeks	0/63	NA	NA
	ADA+MTX		1/65	Acute respiratory distress syndrome	NR
ADORE van Riel 2006	ETN mon	16 weeks	0/159	NA	NA
ADORE	ETN+MTX	16 weeks	3/155	Cardiac arrhythmia that occurred 1 month after the patient discontinued study drugs, second due to cardiac arrest and third due to massive cerebral haemorrhage	All considered to be unrelated to study drugs by the investigator
CREATE IIb Keyston	DMARD + PBO	24 weeks	0/65	NA	NA
	ETN50 + DMARD	24 weeks	0/64	NA	NA

e 2012					
ETN309	SSZ + PBO	24 weeks	0/50	NA	NA
	ETN + PBO	24 weeks	0/103	NA	NA
	ETN + SSZ	24 weeks	0/101	NA	NA
RACAT	MTX + SSZ + HCQ on treatment analysis n=222 (some patients exposed to both treatments throughout trial)	48 weeks	0/222	NA	NA
	ETN50 + MTX on treatment analysis n=219 (some patients exposed to both treatments throughout trial)	48 weeks	n=1 (0.5%) originally randomised and received MTX+SSZ+ HCQ, switched to ETN50+MTX	Pneumonia	NR
Weinblatt 1999	PBO + MTX	24 weeks (and 30 days after treatment)	0/30	NA	NA
Weinblatt 1999	ETN 25mg twice weekly + MTX	24 weeks (and 30 days after treatment)	0/59	NA	NA
Weinblatt 1999 [115]	ETN+MTX or MTX+PBO followed by	3 year LTE	1/79	myocardial infarction	NR

	ETN+MTX				
APPEAL	MTX + DMARD (SSZ, HCQ or LEF)	16 weeks	0/103	NA	NA
	ETN + MTX	16 weeks (study RCT endpoint)	1/197 (0.5%)	Gastrointestinal haemorrhage thought to be result of NSAID therapy following accidental fall and pelvic fracture	No
GO-FORTH	PBO + MTX	24 weeks	0/88	NA	NA
	GOL + MTX	24 weeks	0/86	NA	NA
GO-FORWARD	PBO + MTX	24 weeks	0/133	NA	NA
	GOL + MTX	24 weeks	0/89 (1 death in unlicensed GOL 100 mg every 4 weeks arm (ileus, aspiration pneumonia and death from sepsis)	NA	NA
Kay 2008	PBO + MTX (crossover to IFX + MTX at week 20)	52 weeks	0/35	NA	NA
	GOL + MTX	52 weeks	0/35	NA	NA

Abe 2006	PBO + MTX	14 weeks	0/47	NA	NA
	IFX + MTX	14 weeks	0/49 (2 deaths but not in 3 mg/kg extracted dose (both due to pneumonia))	NR	NR
Abe 2006	PBO group crossover to IFX	To week 36 of LTE	NA	NA	NA
	IFX + MTX	To week 36 of LTE	0/129	NA	NA
ATTRACT [375]	PBO + MTX	LTE 102 weeks	4/88 (4.5)	Left ventricle rupture resulting in cardiopulmonary arrest, intestinal gangrene, arrhythmia and cardiopulmonary failure	Judged to be unrelated to study drug
	IFX + MTX	LTE 102 weeks	3/86 (3.5)	Not reported separately for extracted arm	NR
START	PBO + MTX	22 weeks	1/361	Septic shock	NR
	IFX + MTX	22 weeks	0/360	NA	NA
Swefot [140]	SSZ + HCQ + MTX	24 months	0/130	N	NA
	IFX + MTX	24 months	1/128 (0.8)	Complications of acute myeloid leukaemia	NR
ACT-RAY	TCZ + oral PBO	To week 52	2/276 (0.7)	Causes of death in 4 patients: sepsis, septic shock preceded by	NR

				scrotal abscess, skin necrosis, acute renal failure and congestive heart failure, myocardial infarction, and sepsis with meningitis.	
	TCZ + MTX	To week 52	2/277 (0.7)	NR	NR
Nishimoto 2004	PBO	12 weeks	0/53	NA	NA
	TCZ	12 weeks	1/55 (1.8)	Due to reactivation of chronic Epstein Barr virus and consequent haemophagocytosis syndrome 61 days after single dose of TCZ 8 mg/kg i.v.	NR
TOWARD	PBO i.v. + stable cDMARDs	24 weeks	2/413 (0.5)	Pneumonia, intestinal obstruction	NR
	TCZ + stable DMARDs	24 weeks	2/803 (0.3)	Haemorrhagic stroke, postprocedural complications from triple coronary artery bypass graft	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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