Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only (review of technology appraisal guidance 130, 186, 224, 234 and a part review of technology appraisal guidance 225 and 247)

19th October 2012

1. Title of the project:

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only (review of technology appraisal guidance 130, 186, 224, 234 and a part review of technology appraisal guidance 225 and 247)

2. Name of TAR team and project 'lead'

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield.

Lead: Matt Stevenson, Professor of Health Technology Assessment,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 2220691
Fax: 0114 272 4095
Email: m.d.stevenson@sheffield.ac.uk

Address for correspondence

All correspondence should be sent to the Project Lead (Matt Stevenson, m.d.stevenson@sheffield.ac.uk), the Managing Director of ScHARR-TAG (Eva

Kaltenthaler, e.kaltenthaler@sheffield.ac.uk) and the Project Administrator (Gill Rooney, g.rooney@sheffield.ac.uk).

3. Plain English Summary

Rheumatoid arthritis is an inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. It is a systemic disease and can affect the whole body, including the lungs, heart and eyes. In patients with established and aggressive disease, most joints will be affected over time.[1] Rheumatoid arthritis is usually a chronic relapsing condition that has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive. Rheumatoid arthritis has a severe impact on quality of life and it is estimated that approximately one-third of people stop work within two years of onset because of the disease, and this prevalence increases thereafter.

It has been estimated that approximately 1% of the population have rheumatoid arthritis.[2,3] In NICE Technology Appraisal 195 it was estimated that approximately 15% have severe disease.[4] Rheumatoid arthritis affects three times as many women as men and has a peak age of onset of 40–70 years.[5]

There is no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. Treatment for rheumatoid arthritis usually includes: non-steroidal anti-inflammatory drugs (NSAIDS), which reduce pain, fever and joint swelling/inflammation, and disease modifying anti-rheumatic drugs (DMARDs). DMARDs may be broadly classed as either conventional or biologic. Conventional DMARDs include methotrexate, leflunomide and sulfasalazine, while the latter group includes, but is not limited to, tumour necrosis factor (TNF) inhibitors. DMARDs slow the disease process and reduce joint damage. Corticosteroids may also be used to control inflammation. The main aim of management in early disease is to suppress disease activity and induce disease remission, prevent loss of function, control joint damage, maintain pain control and

enhance self-management.1 In established disease, management should address complications and associated comorbidity, and the impact of the condition on the patient's quality of life.

4. Decision problem

4.1 Purpose of the decision to be made

The assessment will address the question "What is the long-term efficacy, safety, and cost-effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only?"

4.2 Clear definition of the interventions

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.

<u>Mode of action</u>

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 rheumatoid arthritis.

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 rheumatoid arthritis.

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.

Marketing licence and administration method.

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

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

Infliximab (Remicade, Merck Sharp & Dohme), in combination with methotrexate, 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 methotrexate, has been inadequate. It is also licensed for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs. It is administered by intravenous infusion.

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

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

Abatacept (Orencia, Bristol-Myers Squibb) in combination with methotrexate 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 DMARDs including methotrexate or a tumour necrosis factor-alpha inhibitor. It is administered by intravenous infusion and is currently in development for subcutaneous administration. The manufacturer has recently received a marketing authorisation for a subcutaneous formulation of abatacept.

Tocilizumab (RoActemra, Roche), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis 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 methotrexate or where continued treatment with methotrexate is inappropriate. Tocilizumab is administered by intravenous infusion.

4.3 Place of interventions in the treatment pathway

For people with newly diagnosed rheumatoid arthritis, 'Rheumatoid arthritis: the management of rheumatoid arthritis in adults'1 recommends a combination of DMARDs (including methotrexate 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. NICE guidance (TA130, TA186 and TA225)[6,7,8] recommends the use of the TNF inhibitors etanercept, infliximab, adalimumab, certolizumab pegol and golimumab in people with rheumatoid arthritis after the failure of two conventional DMARDs, including methotrexate, and who have a disease activity (DAS28) severity score greater than 5.1. TA247[9] recommends tocilizumab as a potential alternative to TNF-inhibitors in the same circumstances as in TA130,[6] that is in patients with a DAS28 score greater than 5.1, after a trial of two conventional DMARDs. NICE guidance TA234 does not recommend the use of abatacept in people with rheumatoid arthritis after the failure of conventional DMARDs only.[10] Terminated NICE guidance TA224 was unable to issue recommendations for the use of golimumab in people with rheumatoid arthritis that has not been treated with methotrexate.[11] NICE has also issued guidance (TA195, TA225 and TA247)[4,8,9] on the treatment of rheumatoid arthritis after the failure of a TNF inhibitor but this will not be addressed in this appraisal.

4.4 Relevant comparators

The relevant comparators within the final scope differ according to the population considered (see 4.5).

For patients with moderate to severe, or severe, active arthritis that has been previously treated with conventional DMARDs only, the comparators are the interventions themselves, management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDs and corticosteroids, and tofacitinib (subject to NICE guidance).

For patients with severe active rheumatoid arthritis not previously treated with methotrexate, or other DMARDs the comparators are combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide), DMARD monotherapy with dose escalation and the interventions themselves (subject to licence).

4.5 Population and relevant subgroups

The population will comprise three groups:

i) adults with severe active rheumatoid arthritis not previously treated with methotrexate or other DMARDs

ii) adults with severe active rheumatoid arthritis that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate)

iii) adults with moderate to severe active rheumatoid arthritis that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate).

The scope does not specify the definition of severe active rheumatoid arthritis and moderate to severe active rheumatoid arthritis. However, from attendance at the scoping workshop the Assessment Group anticipate that severe active rheumatoid arthritis will be defined by a DAS score of ≥5.1, and that moderate to severe active rheumatoid arthritis will be defined as a DAS score between 3.2 and 5.1 respectively.

The scope issued by NICE has already defined subgroups, as such it is not anticipated that further subgroups would be considered.

4.6 Key factors to be addressed

The review aims to:

- evaluate the clinical effectiveness of each intervention in affecting key outcomes (see 5.2.1.4) 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
- identify key areas for primary research
- estimate the possible overall cost of amending the current provision of interventions in the light of the cost-effectiveness results produced.

4.7 *Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment*

Given the final scope the evaluation of interventions in the following groups are outside of the appraisal scope.

- The initiation of treatment in patients without active RA
- Patients with a DAS score below 3.2 where they have received previous treatment with methotrexate or other DMARDs
- Patients with a DAS score below 5.2 if they have not been previously treated with methotrexate or other DMARDs
- Patients who have been previously treated with one or more biologic DMARDs.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'[12] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[13]

5.1. Search strategy

5.1.1 Search scope

The scope of the search for clinical effectiveness evidence will take into account the following requirements:

- The need to take into consideration the sequencing of treatment
- The potential need to make indirect comparisons, including, if possible a network meta-analysis

For these reasons, the aim of the search, in the first instance, will be to identify all randomised controlled trial evidence of disease modifying treatments for rheumatoid arthritis.

It is envisaged that RCTs may not provide sufficient evidence for some outcomes and for some aspects of disease management. Such examples might include adverse events, discontinuation of or resistance to treatment and long term effectiveness. For these reasons, a subsequent aim of the search will be to identify, where required, evidence from observational studies and disease registers of sufficiently long follow-up and quality.

New searches will be undertaken. These will be informed by search strategies used in previous assessments. Studies identified through the new searches will be cross checked against assessments that have informed previous NICE guidance.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers
- Scrutiny of sponsor submissions and of previous assessments undertaken to inform NICE guidance relevant to the decision problem

5.1.1 Electronic searches

Search strategies will be used to identify relevant studies and systematic reviews/meta-analyses (for the identification of additional trials). Given the broad range of potentially relevant treatments, a simple, inclusive strategy will be used in the first instance, focussing on keywords relating to rheumatoid arthritis and incorporating RCT and systematic review filters. Subsequent searches for observational studies, including disease registers, will be undertaken where required. Searches will not be restricted by publication date or by language. The language restriction will be implemented at the sifting stage in order to gauge the scale and nature of the evidence being excluded on the grounds of language of publication alone. The proposed draft Medline search strategy is provided in Appendix 1. A

comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager© software.

5.1.2 Databases

The following electronic databases will be searched from inception: Medline (Ovid); Medline in Process; CINAHL; EMBASE; the Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, and HTA databases; Science Citation Index (SCI).

Current research registers (e.g. the NIHR CRN Portfolio, Current Controlled Trials, Clinical Trials.gov) will also be searched and relevant professional and research organisations contacted. Citation searches of key included studies will be undertaken using the SCI citation search facility.

In addition TOXLINE will be searched for evidence on safety and adverse events.

5.2 Inclusion/Exclusion criteria

5.2.1 Inclusion criteria

The inclusion criteria are as reported in sections 5.2.1.1-5.2.1.5 below. The review of clinical effectiveness will include any RCT reporting at least one of the outcomes in 5.2.1.4 and any study of sufficiently long duration and quality that reports adverse events. Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be used as sources of references.

5.2.1.1 Population

The population will comprise three groups:

i) adults with severe active rheumatoid arthritis not previously treated with methotrexate or other DMARDs

ii) adults with severe active rheumatoid arthritis that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate)

iii) adults with moderate to severe active rheumatoid arthritis that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate).

The scope does not specify the definition of severe active rheumatoid arthritis and moderate to severe active rheumatoid arthritis. However, from attendance at the scoping workshop the Assessment Group anticipate that severe active rheumatoid arthritis will be defined by a DAS score of ≥5.1, and that moderate to severe active rheumatoid arthritis will be defined as a DAS score between 3.2 and 5.1 respectively.

5.2.1.2 Interventions

For rheumatoid arthritis not previously treated with methotrexate or other DMARDs:

- Adalimumab
- Etanercept
- Infliximab
- Golimumab

For rheumatoid arthritis that has been previously treated with conventional DMARDs only:

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

The above interventions will be assessed as administered in accordance with licensed indications and may be delivered in conjunction with methotrexate or as monotherapy (as specified in licensed indications).

5.2.1.3 Comparators

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

- Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) or DMARD monotherapy with dose escalation
- The interventions will be compared with each other

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

- Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
- The interventions will be compared with each other
- Tofacitinib, subject to NICE guidance

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

- Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
- The interventions will be compared with each other
- Tofacitinib, subject to NICE guidance

5.2.1.4 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

5.2.1.5 Study design

According to the accepted hierarchy of evidence, randomised controlled trials (RCTs) will be included for clinical effectiveness, as they minimise the possibility of bias from confounding factors. If insufficient data are available from RCTs, observational studies or non-randomised trials may be considered. For example this criterion will be relaxed for the consideration of adverse events, discontinuation or resistance to treatment and long term evidence of effectiveness, for which observational studies and disease registers of sufficiently long follow-up and good quality may be included.

5.2.2 Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered methodologically unsound in terms of either study design or the method used to assess outcomes will be excluded from the results. The following publication types will also be excluded from the analysis:

- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.
- Non-English language papers

5.3 Data extraction strategy

Retrieved studies will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in section 5.2. Studies will be assessed for relevance first by title/abstract, and then finally by full text, excluding at each step studies which do not satisfy those criteria; abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality. One reviewer will examine titles and abstracts for inclusion, and a second reviewer will check at least 10% of citations, with a kappa coefficient

calculated to measure inter-rater reliability. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion/exclusion criteria. Data will be extracted by one reviewer using a standardised data extraction form and a second reviewer will check at least 10% of data extraction forms. A draft data extraction form is contained in Appendix 2. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study. Handling data obtained from the manufacturer's submission is detailed in Section 7.

5.4 Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using the Cochrane Risk of Bias tool[14] or (adapted) criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials (RCTs).[12]

5.5 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. If appropriate (i.e. if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using the Cochrane Collaboration ReviewManager© software (version 5.1).[15]
Heterogeneity will be explored through consideration of the study populations, methods, and interventions, by visualisation of the results, and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

If the evidence permits, a network meta-analysis will be undertaken to determine efficacy and safety. This will be populated with all identified trials involving an intervention or a comparator deemed relevant to the decision problem. Where a full

network incorporating all interventions and comparators of interest cannot be constructed, indirect comparisons will be undertaken where applicable.

6 Report methods for synthesising evidence of cost-effectiveness

6.1 *Identifying and systematically reviewing published cost-effectiveness studies*

The sources detailed in section 5 will be used to identify studies of the cost effectiveness of any of the interventions and comparators. Searches will also be undertaken of EconLIT, NHS EED and the websites of HTA organisations including HTAi, INAHTA and ISPOR. Relevant studies identified and included in the manufacturer's submission will also be included. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal checklist for economic evaluations[16] together with the Eddy checklist on mathematical modelling.[17] (see Appendix 3)

6.2 Systematic literature search for other data related to cost-effectiveness

A search of the broader literature on outcomes following treatment with an intervention or comparator will be undertaken to identify the evidence base on HRQoL in relation to key clinical outcomes such as DAS and HAQ scores. The literature search will also attempt to identify any mapping from such measures to preference based utility measures. A further systematic review of the costs associated with RA, will be undertaken. These data will be particularly beneficial if categorised by a clinical outcome measure such as DAS or HAQ. Primary data collection will not be undertaken.

6.3 *Assessment group economic model*

A new economic evaluation is likely to be carried out from the perspective of the UK NHS. The model structure will be determined in consultation with clinical experts. The TAR team has extensive experience and publication track-record using state transition modelling, discrete event simulation, individual patient modelling, meta-modelling, and the use of decision trees in economic evaluation and has some previous experience of modelling treatments for RA. Whilst the decision problem for the appraisal is about the initiation of the first biologic DMARD, the sequenced nature of treatment means that the model will consider subsequent therapies. The subsequent therapies considered will be limited by those that are recommended as options in the guidance provided within the NICE Technology Appraisals 195,[4] 225[8] and 247[9] and will include: rituximab followed by conventional DMARDs; rituximab followed by

tocilizumab followed by conventional DMARDs; and for people for whom rituximab is not suitable, a second biologic DMARD followed by conventional DMARDs.

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both cost and benefits will be discounted at 3.5% per annum.

Cost and utility data from published sources associated with RA will be incorporated into the above model in order to allow the economic, as well as clinical, implications of treatment to be assessed. Ideally, evidence on the impact of these therapies on HRQoL will be available directly from the trials included within the review. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be informed by NICE DSU Guidance.[18]

The key model outputs will be the discounted incremental costs and discounted incremental quality adjusted life years gained for each intervention and comparator in a full incremental analysis. Univariate sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how robust the results of the economic analyses are, given the available evidence. Probabilistic sensitivity analyses will be undertaken to determine how robust the results of the economic analysis are, given the current level of evidence, and to provide a more informative estimation of cost-effectiveness.

7 Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than the 1st of March 2012. Data arriving after this date may not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on economic model submission, will be assessed for clinical validity, reasonableness of assumptions, and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or by developing de-novo modelling.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8 Competing interests of authors

None.

9 Appendices

Appendix 1:

Draft Medline search strategy for the review of clinical effectiveness

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

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1 exp Arthritis, Rheumatoid/

2 rheumatoid arthritis.tw.

3 1 or 2

The above simple strategy will be used in the first instance. The strategy will be combined with search filters, recommended by the CRD guidance on systematic reviews, for the following study designs:

- Randomised controlled trials
- Systematic reviews

Appendix 2: Draft data extraction form

STUDY & DESIGN	DATA EXTRACTION	ADALIMUMAB/ ETANERCEPT/ INFLIXIMAB/ CERTOLIZUMAB PEGOL / GOLIMUMAB / TOCILIZUMAB / ABATACEPT (DELETE AS APPROPRIATE) RCT/CONTROLLED STUDY (CONCURRENT)/CONTROLLED STUDY (HISTORICAL)/UNCONTROLLED STUDY (DELETE AS APPROPRIATE)
Trial	REVIEW DETAILS	
	Author, year	
Study design	**Objective**	
	Study design (e.g. RCT, before-and-after study)	
	Publication type (i.e. full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	INTERVENTIONS	
	Focus of interventions (comparisons)	
	Description	
	Intervention group	
	Drug name/s	
	Dose	
	Frequency	
	Route of administration	
	Control group	
	Drug name/s	
	Dose	
	Frequency	

	Route of administration	
	Geographical Setting	
	Duration of treatment	
	Length of follow-up (if different)	
	STUDY CHARACTERISTICS	
	Method of randomisation	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	
	Blinding level	
	Numbers included in the study	
	Numbers randomised	T1: T2:
	POPULATION CHARACTERISTICS	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean yr.)	
	Gender (% female)	
	Ethnicity	
	DAS score (N.B. severe ≥5.1, moderate—severe 3.2—5.1)	
	Duration of RA ≥	

	Auto-antibody status	
	(Comorbidity) %	
	Previous treatment with conventional DMARDs (including methotrexate)	
	No. of previous DMARDs	
	(Previous DMARD) %	
	On steroids (%)	
	On NSAIDs (%)	
	If on methotrexate - dose?	
	% joint replm	
	Prior TNF inhibitor treatment	
	Reason for discontinuation of TNF inhibitor	
	Eligibility for the previous anti-TNF	
	Doses and treatment duration of previous TNF inhibitor (and concomitant DMARDs)	
	Wash out period from the previous TNF inhibitor	
	Concomitant treatments during the trial	Methotrexate: allowed / not allowed / unclear / conditional: Other DMARDs: allowed / not allowed / unclear / conditional: Steroids: allowed / not allowed / unclear / conditional:
	Other treatments allowed	
	Other treatments not allowed	
	Other relevant information	
	Were intervention and control groups comparable?	

	OUTCOMES	
	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	
	ANALYSIS	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	
	Was attrition adequately dealt with?	
	Number (%) followed-up from each condition	
	RESULTS	
	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	
	Adverse events	
	Deaths	
	Serious adverse events	
	Serious infection (definition)	
	Infections needing antibiotics	
	Any infection	
	Malignancy	
	Injection site reaction	
	Infusion reaction	
	Others	
	Other information	
	SUMMARY	
	Authors' overall conclusions	
	Reviewers' comments	

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluation[16] together with the Eddy checklist on mathematical models employed in technology assessments.[17]

Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

Additional information that is needed by NCCHTA and NICE.

Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

Contact details of TAR team

Matt Stevenson
Professor of Health Technology Assessment and Technical Director of the ScHARR Technology Assessment Group
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA
Tel: 0114 222 0691
Fax: 0114 272 4095
E-mail: M.D.Stevenson@sheffield.ac.uk

Rachel Archer, Research Fellow,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0793
Fax: 0114 272 4095
Email: r.archer@sheffield.ac.uk

Emma Everson-Hock, Research Fellow,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 5205
Fax: 0114 272 4095
Email: e.everson-hock@sheffield.ac.uk

Suzy Paisley, Senior Research Fellow
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0704
Fax: 0114 272 4095
Email: s.paisley@sheffield.ac.uk

Emma Simpson, Research Fellow,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0708
Fax: 0114 272 4095
Email: e.l.simpson@sheffield.ac.uk

Jon Tosh, Research Fellow,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0830
Fax: 0114 272 4095
Email: j.tosh@sheffield.ac.uk

Allan Wailoo, Reader in Health Economics,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0729
Fax: 0114 272 4095
Email: a.j.wailloo@shef.ac.uk

Gill Rooney
Project Administrator
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA
Tel: 0114 222 0800
Fax: 0114 272 4095
E-mail: g.rooney@sheffield.ac.uk

Clinical Advisors:

Professor David L Scott
Professor of Clinical Rheumatology
King's College
London
Email: david.l.scott@kcl.ac.uk
Telephone: 0207 848 5215

One further clinician to be confirmed

Address for correspondence

All correspondence should be sent to the project lead, Matt Stevenson (M.D.Stevenson@sheffield.ac.uk), the managing director of ScHARR-TAG (Eva Kaltenthaler, e.kaltenthaler@sheffield.ac.uk), and the project administrator (Gill Rooney, g.rooney@sheffield.ac.uk).

Timetable/milestones

Milestone	
Draft protocol	19th October 2012
Final protocol	9th November 2012
Progress report	8th March 2013
Draft assessment report	13th May 2013
Final Assessment report	12th June 2013

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