Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of NICE – Final protocol

1. Title of the project

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)

2. Name of TAR team and 'lead'

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3. Plain English Summary

The term axial spondyloarthritis refers to a form of arthritis in which the predominant symptom is back pain due to inflammation of spinal and/or pelvic joints. If definite changes on plain X-rays are present, the disease is classified as ankylosing spondylitis, but if they are absent it is classified as non-radiographic axial spondyloarthritis. Further tests may indicate that in some patients non-radiographic axial spondyloarthritis is very likely to be ankylosing spondylitis, only at an earlier stage of disease.

Conventional therapy for axial spondyloarthritis includes treatment with NSAIDs, exercise, and physiotherapy. Tumour necrosis factor-alpha (TNF-alpha) inhibitors are typically used when the disease has not responded adequately to conventional therapy.

This project will evaluate the evidence relating to the use of five TNF-alpha inhibitor treatments (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), within their respective licensed indications, for treating severe active ankylosing spondylitis, or severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (but with objective signs of inflammation). The objective of this project is to assess the benefits and adverse effects of these TNF-alpha inhibitor agents and to evaluate if their use to treat these patients is a cost-effective use of NHS resources.

4. Decision problem

- **Objectives**

The aim of the study is to determine the clinical effectiveness, safety, and cost-effectiveness of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, within their respective licensed indications, for the treatment of severe active ankylosing spondylitis, or severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (but with objective signs of inflammation). If evidence allows, the clinical- and cost-effectiveness of sequential use of these treatments will also be evaluated.

- **Background**

Spondyloarthritis (SpA) encompasses a heterogeneous group of inflammatory rheumatologic diseases including ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, inflammatory bowel disease-related arthritis and undifferentiated SpA.[1] SpA can be categorised as having predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial SpA (AxSpA), the predominant symptom is back pain (due to inflammation of the sacroiliac joints, the spine, or both) but there may also be extra-articular and peripheral joint manifestations. There is often a delay of many

years between patients first noticing symptoms, and receiving a diagnosis of SpA. Many people with AxSpA have AS, though the stage of disease (when diagnosed with AS) can vary. In patients with AS, joints and bones may fuse together (over a long period of time) causing restricted movement. This is an indication of later-stage disease.

According to the Assessment of SpondyloArthritis International Society (ASAS) criteria, if radiographic evidence of joint damage (erosions or fusion) due to sacroiliitis is evident, the disease can be classified as AS. If sacroiliitis is not evident on x-rays, but can be demonstrated by other imaging modalities (i.e. evidence of inflammation on MRI scanning) the disease is classified as non-radiographic AxSpA (nr-AxSpA).[2]

Patients with nr-AxSpA may, or may not, have signs of sacroiliac joint inflammation on an MRI scan. There may be other objective signs of inflammation such as an abnormally raised erythrocyte sedimentation rate (ESR) and C-Reactive protein (CRP) level, though these are less sensitive and specific for AS. Active inflammation based on MRI is commonly given equivalent weight to X-ray evidence.[3] The use of MRI allows for earlier detection of the disease, since joint damage may not become evident on X-rays for many years. An MRI diagnosis may therefore provide the opportunity for treatment to reduce the possibility of long-term structural damage (and associated burden of symptoms).[3]

Currently, only limited epidemiological data are available for AxSpA defined according to ASAS. For AS, the prevalence is thought to range from 0.05% to 0.23%, with a prevalence of 0.25% in European populations.[4] It is around three times more common in men than in women.[5] A recent study published in the US reported an estimated AS prevalence of 0.52-0.55%, and the prevalence of AxSpA as approximately 1.0-1.4%.[6] The proportion of nr-AxSpA among patients with AxSpA is estimated to be between 20-80%.[7] Each year in the UK, an estimated 2% of patients present to general practice with back pain, and up to 5% of these will show features of AS.[8] In addition, AS is associated with an increased risk of death: it is estimated that patients have a standardised mortality ratio of 1.5 or greater. According to BSR guidelines, the excess mortality is mainly accounted for by cardiac valvular disease, amyloidosis and fractures.[9] Most patients with AS develop the first symptoms at 25-45 years of age.[10] Non-radiographic AxSpA affects approximately equal numbers of men and women, but men are more likely to develop radiographically evident disease. People with SpA often have the genetic marker human leukocyte antigen (HLA)-B27.

Short- and long-term treatment goals for AxSpA include minimising pain and stiffness, maintaining function and posture, arresting disease progression and maintaining quality of life and ability to work. Current conventional therapy for AxSpA includes acute anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy and exercise.

- **Interventions**

Tumour necrosis factor-alpha (TNF-alpha) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy. They target the activation of tumour necrosis factor-alpha (TNF-alpha) and its subsequent activation of downstream inflammatory processes, and as such have the potential to offer symptom control as well as altering disease progression. Adalimumab, certolizumab pegol, golimumab and infliximab are monoclonal antibodies, whereas etanercept is a recombinant human TNF receptor fusion protein.

Adalimumab, etanercept, golimumab and infliximab are licensed in the UK for the treatment of adults with severe active AS that has responded inadequately to conventional therapy. Certolizumab pegol is licensed for the treatment of adults with severe active AS whose disease has responded inadequately to, or who are intolerant of, NSAIDs.

Adalimumab and certolizumab pegol are also licensed for the treatment of adults with severe nr-AxSpA with objective signs of inflammation (including elevated C-reactive protein (CRP) and/or

positive MRI), whose disease has responded inadequately to, or who are intolerant of NSAIDs. Etanercept, golimumab and infliximab do not currently have a UK marketing authorisation for nr-AxSpA, although it is anticipated that authorisation for etanercept and golimumab will be granted by the time of the NICE appraisal.

Current NICE guidance recommends treatment with adalimumab, etanercept and golimumab in adults with active (severe) AS only if certain criteria are fulfilled, but it does not recommend infliximab for AS.[9, 11]

- **Previous NICE appraisals**

In the previous NICE Technology Appraisal TA143, adalimumab, etanercept and infliximab were evaluated for AS, while in TA233 golimumab was evaluated for AS. A number of key areas of uncertainty and potential limitations of the evidence base were identified from these appraisals. These include:

1. A lack of direct head-to-head trial evidence evaluating the relative efficacy and safety of the TNF-alpha inhibitors;
2. A lack of evidence on the efficacy and safety of the sequential use of TNF-alpha inhibitors;
3. The long-term effectiveness of TNF-alpha inhibitors in controlling disease activity;
4. The rate of disease progression in responders and non-responders to treatment, and those on placebo;
5. The proportion of patients who may experience a significant improvement in their condition without TNF-alpha inhibitor treatment;
6. The rate of treatment withdrawal on TNF-alpha inhibitors and the degree to which a patient's condition might be expected to rebound if therapy is withdrawn;
7. The adverse effects associated with the long-term use of TNF-alpha inhibitors;
8. The impact of TNF-alpha inhibitors on the progression of structural damage in the spine and functional disability associated with ankylosis;
9. The time horizon appropriate for considering the cost-effectiveness of TNF-alpha inhibitors;
10. A lack of registry data of patients receiving TNF-alpha inhibitors for severe active AS.

It is envisaged that the appraisal of the clinical- and cost-effectiveness of TNF-alpha inhibitors for AS and nr-AxSpA will consider each of these areas of uncertainty and identify the relevant evidence available to inform the limitations of the previous appraisals.

5. Report methods for synthesis of evidence of clinical effectiveness

The protocol details will be submitted for registration on PROSPERO, an international database of prospectively registered systematic reviews in health and social care (http://www.crd.york.ac.uk/prospero/). A systematic review of the clinical effectiveness will be performed following the general principles recommended in CRD's guidance and the PRISMA statement.[12, 13]

A best evidence synthesis approach will be applied to the additional assessment questions: systematic methods will be used to identify studies, although full systematic review methodology will not be undertaken for every question. This approach will be similar to the one used in a recent systematic review and economic evaluation performed by CRD and CHE.[14]

- **Search strategy**

Searches of electronic databases will be conducted to identify relevant randomised controlled trials (RCTs) of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab for ankylosing spondylitis or axial spondyloarthritis. Searches for studies in patients with axial spondyloarthritis will not be limited by date. Searches for studies in patients with AS will be run from 2005 to update the previous assessment, though searches for studies of golimumab and certolizumab pegol for AS will not be date-restricted.[15] In addition, relevant published systematic reviews and trial registers will be

searched to identify any further RCTs. The draft MEDLINE search strategy for the review of clinical efficacy is provided in the appendix. This will be converted to run appropriately on other databases.

In the first instance, information on adverse events will be identified from searching resources of the US and European drug regulatory agencies (i.e. FDA, EMEA). Where additional information is required, the additional searches for evidence on serious adverse events will not be restricted by date or study design.

Searches of electronic databases will be conducted as necessary to identify relevant sources of information on the natural history and mortality rates associated with AS and AxSpA and on the long-term effectiveness and sequential use of anti-TNF agents.

The following resources will be searched: MEDLINE, MEDLINE In-Process, Cumulative Index to Nursing & Allied Health (CINAHL), EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, and Cochrane Central Register of Controlled Trials (CENTRAL). Searches of electronic databases will not be restricted by language or study type.

In addition to utilising information and data from the company submissions, information on studies in progress, guidelines, unpublished research or research reported in the grey literature will also be sought by searching a range of relevant databases including Conference Proceedings Citation Index- Science, PROSPERO, National Guideline Clearinghouse, NHS Evidence, NHS Clinical Knowledge Summaries, and ClinicalTrials.gov. At the time of receiving the company submission, update searches will be conducted to ensure the review remains up-to-date and covers all relevant evidence at the time of submission. See appendix for details of searching.

- **Inclusion and exclusion criteria**

Two reviewers will independently screen all titles and abstracts. Full manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed by two reviewers according to the criteria below. Any discrepancies will be resolved by consensus and, if necessary, a third reviewer will be consulted. Studies available only as abstracts will be included and attempts will be made to contact authors for further data.

Study design

For the review of clinical efficacy RCTs will be eligible (including any open-label extensions of RCTs).

Information on adverse events will also be sought from regulatory sources. If further adverse events data are needed they will be sought from suitably large studies.

To address the questions of mortality rates, natural history, long-term effectiveness, adherence, and sequential use, published analyses based on large and long-term data sets (including studies of registry data) will also be eligible.

Interventions

Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are the relevant interventions.

Comparators

Relevant comparators are conventional management strategies (either with or without placebo) and also the different TNF-alpha inhibitors listed above (i.e. head-to-head trials) will also be eligible.

Participants
Studies of adults who have either of the following diagnoses will be considered:

- Severe active ankylosing spondylitis
- Severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation (such as elevated C-reactive protein levels or a positive MRI scan)

Patients with predominantly peripheral spondyloarthritis will be excluded.

For the review of the clinical efficacy of anti-TNFα agents we will focus on studies of patients whose disease has responded inadequately to, or who are intolerant to, non-steroidal anti-inflammatory drugs (NSAIDs) will be eligible. Patients who are contraindicated to receive NSAIDs will also be eligible.

Outcomes
Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness will be extracted. The eligible outcomes will be:

- Multiple domain response criteria: (e.g. ASAS 20, ASAS 40, ASAS 5/6 and ASAS partial remission)
- Disease activity (e.g. BASDAI)
- Functional capacity (e.g. BASFI)
- Disease progression (e.g. mSASSS)
- Pain (e.g. VAS scores)
- Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis)
- Symptoms of extra-articular manifestations (including anterior uveitis, inflammatory bowel disease and psoriasis)
- Health-related quality of life (e.g. EQ-5D)
- Rates of treatment discontinuation and withdrawal
- Adverse events

Our evaluation of the regulatory data will specifically focus on the known serious adverse events of these agents: malignancies, severe infections (i.e. those that require intravenous antibiotic therapy and/or hospitalisation, or cause death) and reactivation of latent tuberculosis. If additional serious adverse events have been reported to regulatory bodies, then the incidence of these will also be assessed. Data relating to serious adverse effects associated with anti-TNF agents in indications other than axSpA will also be considered, provided it is clinically appropriate to do so.

- **Data extraction strategy**

Data relating to both study design and quality will be extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made where possible to contact authors for missing data. Data from studies with multiple publications will be extracted and reported as a single study.

To avoid unnecessary duplication of work, data from tables published in previous NICE technology appraisal reports (TA143 and TA233) will be used, with additions made where appropriate.

- **Quality assessment strategy**

The quality of RCTs will be assessed using the Cochrane risk of bias tool, with additional assessments made for baseline imbalance of important prognostic indicators.[16, 17] The relevant prognostic and treatment response indicators will be identified from both published research and clinical advice. The risk of bias assessments will be performed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted.

The quality of non-randomised studies will be assessed using a checklist based on CRD Guidance[12] and used in other technology assessments for NICE.[14]

- **Methods of analysis/synthesis**

The analysis and synthesis of clinical data in this review will be conducted in distinct sections. In the first instance the results of the data extraction in terms of study characteristics and quality assessment will be presented in a series of structured tables and summarised narratively. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated. If necessary, sensitivity analyses will be undertaken when possible. Evidence relating to the potential short- and long-term benefits of the anti-TNFα agents on both AS and nr-AxSpA will be investigated and synthesised using accepted methods. The serious adverse effects of these agents will also be explored.

It is anticipated that trials conducting head-to-head comparisons of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab for AS and AxSpA will not be available. Therefore, if feasible and appropriate, indirect and/or mixed treatment comparisons will be conducted using Bayesian statistical methods to provide information on the benefits of the active treatments relative to the appropriate comparators and each other.[18] Meta-analysis using mixed treatment comparisons enables the estimation of different parameters (e.g. ASAS20/40, BASDAI, BASFI) from several studies with similar comparisons to be combined when direct evidence on comparisons of interest is absent or sparse.[19] For example, the five active treatments being evaluated are expected to all have a common comparator of placebo, which will allow the network between the anti-TNFs to be established and provide information on the benefits of these treatments relative to placebo, and to each other.

6. Report methods for synthesising evidence of cost-effectiveness

Searches will be used to identify studies of the cost-effectiveness of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab for the treatment of AS and AxSpA. The searches will be undertaken in NHS Economic Evaluation Database (NHS EED). Additional searches will be undertaken as necessary in the databases listed in Section 5. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond *et* al.[20] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Care Excellence (NICE).[21] This information will be tabulated and summarised within the text of the report. In particular information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

As discussed in Section 4, a number of key areas of uncertainty were identified in the review process of TA143 and TA233, which the current assessment will attempt to address where sufficient data are available. It is anticipated that three additional reviews will be undertaken to inform the economic evaluation of TNF-alpha inhibitors in the treatment of AS and nr-AxSpA:

1. The long-term effectiveness of TNF-alpha inhibitors in AS and nr-AxSpA. For the cost-effectiveness assessment in TA143 and TA233, assumptions regarding the long-term extrapolation of the rate of disease progression in responders and non-responders to treatment and the proportion of patients who experience an improvement in their condition without TNF-alpha inhibitors were key drivers of the cost-effectiveness of the agents. Furthermore the disease-modifying effect of these agents on functional disability and the progression of structural damage within the spine were uncertain in the previous evaluations. A systematic literature search will be undertaken to identify studies reporting the natural history associated with AS and nr-AxSpA and the long-term effectiveness of TNF-alpha inhibitors in controlling disease activity. This review will also aim to identify the rate at which patients are expected to withdraw from TNF-alpha treatments.

2. Health-related quality of life associated with disease progression. It is expected that measures of disease progression will be expressed in terms of multiple domain response criteria (e.g. ASAS 20/50/70) and instruments of disease activity and functional capacity (e.g. BASDAI, BASFI). In accordance with the NICE reference case, utility values should be based on the EuroQoL – EQ5D instrument. Therefore a systematic review of utility studies will be carried out to identify relevant studies which i) directly estimate EQ-5D utility values; and ii) establish the relationship between generic measures of utility (in particular, the EQ-5D) and measures of disease progression (including mapping studies).

3. Resource use and direct health care costs associated with AS and nr-AxSpA in the UK. A systematic review will be undertaken to identify studies reporting the direct health care resources utilised by AS and nr-AxSpA patients in the UK and any studies which establish the relationship between health care costs and disease activity. The inclusion criteria for studies will be restricted to those which report data in the UK only.

The presence of any additional data gaps that may need to be filled during the development of the model will be identified and additional searches may be required. We will also work with our clinical advisors at the start of the project to identify relevant UK data sources such as The British Society for Rheumatology Biologics Register for AS (BSRBR-AS), and will make contact with the relevant investigators with a view to securing access to this data should this be required.

- **Development of a new decision-analytic model**

A new decision-analytic model will be developed to estimate the cost-effectiveness of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab for the treatment of active (severe) AS and nr-AxSpA. The model will be developed in accordance with the NICE reference case. The model will have a lifetime horizon and consider costs from the perspective of the National Health Services and Personal Social Services. Both costs and quality-adjusted life years (QALYs) will be discounted at 3.5% per annum.

Where sufficient data permits an analysis, the cost-effectiveness assessment will also explore the sequential use of treatments as this was identified as an important area of uncertainty in the previous appraisal (TA143). It is envisaged that the cost-effectiveness of sequential therapy with TNF-alpha inhibitors will consider: i) a comparison of sequential treatment strategies with a single agent strategy, ii) different sequential treatment strategies compared with one another, i.e. an assessment of the relative cost-effectiveness of the different sequences of treatment, and iii) the circumstances when an

alternative TNF-alpha inhibitor might be a cost-effective option, e.g. in patients who have not had an adequate response, or who are intolerant to, one of the therapies.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies on the chronic inflammatory conditions, in a way that is clinically acceptable.
- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts.
- To relate initial and intermediate outcomes (such as response to treatment and functional status) to final health outcomes, expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the mean cost-effectiveness of each of the therapies based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty*, is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, *decision uncertainty*. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- To use scenario analysis to explore the sensitivity of the cost-effectiveness results to changes in the structural assumptions of the model and the time horizon over which the treatments are assessed, which was identified as an area of uncertainty in TA143.

The specific details of the data to be used to populate the model will have to await the development of the structure, the systematic searches of the literature and the manufacturers' submissions. However, we expect to derive estimates of the relative effectiveness of the therapies from available randomised trials. Estimates of the natural history progression of AS and nr-AxSpA, and patients' prognosis if they continue or withdraw from treatment may use observational evidence relevant to UK clinical practice (e.g. BSRBR-AS registry) identified by the review of clinical effectiveness.

Depending upon the limitations of the available data, it may be necessary to consider expert elicitation with a sample of UK rheumatology experts in AS and AxSpA in order to generate prior estimates of unknown parameters in the model (e.g. the effect of withdrawal from anti-TNFs). If this is necessary, an interactive elicitation exercise will be designed to generate estimates of the relevant unknown parameters. Mathematical approaches to elicitation will be applied to quantify the uncertainty using a histogram approach and linear opinion pooling will be applied to combine the separate experts' responses. [22]

7. Handling the company submissions

All data submitted by the drug manufacturers will be considered if received by the review team no later than 10th September 2014. Data arriving after this date will only be considered if time constraints allow.

If efficacy and/or adverse effects data meet the inclusion criteria for the review then they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any economic evaluations included in the company submission will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Clarification on specific aspects of the model may be sought from the relevant manufacturer. An assessment of any differences between the published economic evaluations, those submitted by the manufacturers and any economic evaluation developed by us will be reported.

Any 'commercial in confidence' and 'academic in confidence' data taken from a company submission will be clearly marked in the NICE report (*underlined and followed by an indication of the relevant company name e.g. in brackets)* and removed from the subsequent submission to the HTA.

8. Competing interests of authors

Lesley Kay has been a paid speaker for Pfizer and participated in advisory boards for UCB and Roche.

9. References

1. Lipton SA, Deodhar. The new ASAS classification criteria for axial and peripheral spondyloarthritis. *International Journal of Clinical Rheumatology* 2012;**7**:675-82.
2. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;**68**:777-83.
3. Goh L, Samanta A. Update on biologic therapies in ankylosing spondylitis: a literature review. *International Journal of Rheumatic Diseases* 2012;**15**:445-54.
4. Reveille JD, Sims A-M, Danoy P, Evans DM, Leo P, Pointon JJ, et al. Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. *Nat Genet* 2010;**42**:123-U47.
5. *NHS Choices website: Ankylosing spondylitis* NHS Choices; [cited 2014 29 April]. Available from: http://www.nhs.uk/conditions/Ankylosing-spondylitis/Pages/Introduction.aspx.
6. Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. *Am J Med Sci* 2013;**345**:431-6.
7. Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: New definition of an old disease? *Arthritis Rheum* 2013;**65**:543-51.
8. *NICE Clinical Knowledge Summaries website: Ankylosing spondylitis: Prevalence*. NICE; [cited 2014 29 April]. Available from: http://cks.nice.org.uk/ankylosing-spondylitis#!backgroundsub:2.
9. *Technology Appraisal TA143: Ankylosing spondylitis - adalimumab, etanercept and infliximab*. London: National Institute for Health and Clinical Excellence (NICE); 2008. Available from: http://www.nice.org.uk/TA143
10. Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007;**369**:1379-90.
11. *Technology Appraisal TA233: Ankylosing spondylitis - golimumab*. London: National Institute for Health and Clinical Excellence (NICE); 2011. Available from: http://guidance.nice.org.uk/TA233
12. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination, University of York; 2009. Available from: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf
13. *PRISMA Statement website*. [cited 2014 1 May]. Available from: http://www.prisma-statement.org/.
14. Norman G, Faria R, Paton F, Llewellyn A, Fox D, Palmer S, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Technol Assess* 2013;**17**.
15. McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**:1-158, iii-iv.
16. Higgins JPT, Altman DG, Gotzsche PC, Jueni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**.

17. Corbett MS, Higgins JPT, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods* 2014;**5**:79-85.
18. Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. *Pharmacoeconomics* 2008;**26**:753-67.
19. Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Stat Med* 1996;**15**:2733-49.
20. Drummond M, Sculpher MT, G., O'Brien BJ, Stoddart G. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.
21. *Guide to the methods of technology appraisal 2013* London: National Institute for Health and Clinical Excellence (NICE); 2013. Available from: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf
22. O'Hagan A, Buck CE, Daneshkhah A, Eiser JR, Garthwaite PH, Jenkinson DJ, et al. *Uncertain Judgements: Eliciting Experts' Probabilities*. Chichester: Wiley; 2006.

Appendix: Literature searching

The following draft strategy was designed to identify RCTs in MEDLINE. The strategy will be adapted to run on other databases.
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Date of search: 1st May 2014

terms for population
1 spondylarthritis/ or spondylitis, ankylosing/ (12291)
2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (10227)
3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (398)
4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (449)
5 1 or 2 or 3 or 4 (14759)
terms for interventions
6 (adalimumab or humira or 331731-18-1).af. (3641)
7 (certolizumab or CDP870 or cimzia or 428863-50-7).af. (476)
8 (etanercept or enbrel or altebrel or 185243-69-0).af. (5458)
9 (golimumab or CNTO 148 or simponi or 476181-74-5).af. (310)
10 (infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13).af. (8997)
11 6 or 7 or 8 or 9 or 10 (13689)
terms for RCTs
12 randomized controlled trial.pt. (371681)
13 controlled clinical trial.pt. (88214)
14 randomized.ab. (291517)
15 placebo.ab. (153153)
16 drug therapy.fs. (1690846)
17 randomly.ab. (211352)
18 trial.ab. (302552)
19 groups.ab. (1346337)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3319478)
21 animals/ not (animals/ and humans/) (3836647)
22 20 not 21 (2846573)
23 5 and 11 and 22 (978)