National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with conventional 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)

Response to consultee and commentator comments on the remit and draft scope (updated)

Section 1: the draft scope

Section	Consultees	Comments	Action
Background information	Abbott	No comments to add	Comment noted. No action required.
	Healthcare Improvement Scotland	Fine	Comment noted. No action required.
	National Rheumatoid Arthritis Society	NRAS disputes the size of the population quoted in the background information section. The UK wide population figure for the estimated number of people living with Rheumatoid Arthritis is 690,000, as opposed to the 580,000 figure quoted in the document. The number of people living with the disease in England is 580,000 people. The background section neglects to mention the fact that rheumatoid arthritis is a complex disease to manage and that non-drug therapies play an important role in helping to manage the disease; often requiring access to multidisciplinary services such as physiotherapy, podiatry, occupational therapy and pschycological services.	Comment noted. The background section of the scope provides an overview of the condition. Further information about the condition and its management should be included in any submissions to NICE.
	Pfizer Ltd	We consider it appropriate for NICE to re-appraise etanercept and the other	Comment noted. The

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		TNF-alpha inhibitors and welcome the opportunity to present evidence in the populations within our licensed indication. We note the previous NICE guidances (TA130, TA186 and TA225) which recommend the use of TNF-alpha inhibitors in severe RA (disease activity (DAS28) severity score of greater than 5.1).We also note the current BSR guidance [Deighton C et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology (Oxford) 2010 49(6):1197-9] that TNF-alpha inhibitors are recommended in moderate to severe disease, as outlined in recommendation 1: Biological therapies are recommended as options for the treatment of adults who have the following characteristics: (i) active RA as measured by DAS28>3.2 with at least three or more tender and three or more swollen joints; and (ii) have undergone trials of two DMARDs, including MTX (unless contraindicated). A trial of DMARDs is defined as at least two DMARDs usually given concurrently over a 6-month period, with 2 months at standard doses, unless significant toxicity has limited the dose or duration of treatment. Therefore, we suggest that this re-appraisal should review any new evidence in a moderate to severe population and reconcile the divergence in the current BSR and NICE guidance around patients eligible to receive biologic therapy. We feel that this is relevant information and should be captured in the background section to the scope. Accordingly, we suggest the prevalence estimates in the draft scope should be updated to represent both a moderate to severe population and a severe RA population.	population in the scope has been amended to specify separately a group of people with moderate to severe disease.
	Primary Care Rheumatology	We consider that reference should be made to the National Audit Office report "Services for people with rheumatoid arthritis" (2009) which showed	Comment noted. The background section of the

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	Society	that earlier treatment of rheumatoid arthritis would cost the NHS more, but this would be outweighed by productivity gains and less sick leave. The NAO also estimated that after 9 years, earlier treatment would be cost-neutral.	scope provides an overview of the condition. Further information about the impact of the condition should be included in any submissions to NICE. The appraisal will be completed within the published methods of NICE technology appraisal, consideration of productivity costs are beyond the remit of NICE.
	Roche Products	Currently, the background section refers to NICE TA 247 using wording which could be interpreted to mean that tocilizumab is only recommended by NICE for use in TNF inadequate responding (IR) patients. As the recommendations in TA 247 cover the use of tocilizumab in a) DMARD-IR, b) after the failure of one or more biologics, c) after the failure of rituximab, we would recommend that the background section be updated to reflect the TA 247 guidance in full. The description of the technologies listed in the draft scope are accurate. For reasons discussed in the 'population' section below, we consider that tocilizumab should be added to the draft scope with the following description of the techonology: Tocilizumab (RoActemra, Roche Products) is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6). Reducing the activity of IL-6 may reduce inflammation in the joints, prevent long-term damage, improve quality of life and function, and relieve certain systemic effects of rheumatoid arthritis. Tocilizumab, in combination with methotrexate, has a UK marketing	Comment noted. The sentence describing tocilizumab as a possible alternative to a TNF inhibitor in the same context as described in TA130 has been clarified. The MTA will include a partial review of TA 247, for tocilizumab for people whose disease has not responded adequately to, or who were intolerant of, one or more conventional DMARDs only.

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		authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has not responded adequately to, or who were intolerant to, previous therapy with one or more DMARDs or TNF-α antagonists. In these people, tocilizumab can be given as monotherapy in case of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate.	
	Royal College of Pathologists	Accurate information	Comment noted. No action required.
	ScHARR-TAG	As far as I am aware	Comment noted. No action required.
	The Royal College of Nursing	We welcome the proposal form NICE to review the multi technology appraisal .	Comment noted. No action required.
The technology/ intervention	Abbott	Yes	Comment noted. No action required.
	AstraZeneca UK Ltd	Clarification is required whether the intervention is to be appraised in combination or monotherapy.	Comment noted. The appraisal will consider the products within their licensed indications including combination and mono-therapy as indicated.
	Healthcare Improvement Scotland	Yes	Comment noted. No action required.
	Pfizer Ltd	While we accept that all the technologies included in the draft scope are	Comment noted.

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		TNF-alpha inhibitors, etanercept is the only human TNF-receptor fusion protein, unlike the other interventions, which are monoclonal antibodies or fragments thereof. These differences in structure may have an impact on patient outcomes. In addition, we think that it would be useful to clarify interventions that can be used in combination with methotrexate or as a monotherapy within the draft scope as determined by their licensed indication.	Differences between the products in terms of patient outcomes will be considered in the appraisal. Comment noted. The appraisal will consider the products within their licensed indications including combination and mono-therapy as indicated.
	Primary Care Rheumatology Society	Yes	Comment noted. No action required.
	Roche Products	Under the indication for 'rheumatoid arthritis not previously treated with DMARDs', we note that two of the treatments do not have the marketing authorisation for this indication (adalimumab and etanercept). Both treatments are restricted in their early RA licence to patients with severe disease, not previously treated with methotrexate.	Comment noted. All technologies will be appraised within their licensed indications. For etanercept, adalimumab and golimumab this will be disease not previously treated with methotrexate.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	ScHARR-TAG	As far as I am aware	Comment noted. No action required.

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Population	Abbott	Yes, although it may be worth stating explicitly in the scope the definition of moderate disease activity as DAS28>3.2 and severe disease activity as DAS28>5.1 in accordance with the EULAR guidelines.	Comment noted. The population in the scope has been amended to specify separately a group of people with moderate to severe disease. The scope is intended to provide guidance on the populations to be considered but their definition will be considered as part of the appraisal.
	Healthcare Improvement Scotland	The case for early biologic use in patients who are MTX naïve but with adverse prognostic features should be considered	Comment noted. Attendees at the scoping workshop noted that prognostic factors of worse outcomes had been identified. However, they considered that evidence would be in small patient numbers when also combined with consideration of moderate and severe disease.
	MSD Ltd	The appropriate subgroups for severity of disease activity should be: - moderate - moderate to severe. There is benefit to a wider patient population of assessing cost effectiveness in these sub-groups.	Comment noted. The population has been amended to include patients with moderate to severe disease.

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	National Rheumatoid Arthritis Society	The disease has a huge impact on families and carers looking after people with rheumatoid arthritis. NRAS believes the scope should therefore include consideration of the impact of these treatments on these additional societal groups. In our Family Matters survey (2012) 57 per cent reported that RA had a negative or very negative impact on their household income, 41 per cent reported difficulties in their relationship as a result of RA and 93 per cent said that their partner's RA affected their own mood and mental wellbeing. There is also increasing evidence that people with moderate disease (DAS scores between 3.2 to 5.1) can obtain significant health gains via obtaining earlier access to TNF inhibitors. NRAS would like to see the scope include specific consideration of how these treatments impact upon this sub-group.	Comment noted. The population in the scope has been amended to specify separately a group of people with moderate to severe disease. The HRQOL impact to people providing care for patients with RA may be considered as part of the appraisal and economic analysis.
	Pfizer Ltd	We suggest the following revisions to the populations stated in the scope to reflect the licensed indications of the TNF-alpha inhibitors: Adults with severe rheumatoid arthritis not previously treated with DMARDs. Adults with severe rheumatoid arthritis that has not responded to conventional DMARDs only; including methotrexate (unless contraindicated or inappropriate). In addition, we note that NICE has included moderate to severe patients as a sub-group to be appraised. We believe there is sufficient new evidence to consider moderate to severe disease as a third population within the scope. We suggest the following wording for this population: Adults with moderate to severe rheumatoid arthritis that has not responded adequately to conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate).	Comment noted. The population in the scope has been amended to specify separately a group of people with moderate to severe disease whose rheumatoid arthritis has not responded adequately to conventional DMARDs only.
	Primary Care Rheumatology Society	We would like to see consideration of extending treatment with biologics to groups with a DAS-28 score <5.1 in line with the recommendations of the British Society for Rheumatology Guidelines (doi:10/rheumatology/keq006b).	Comment noted. The population in the scope has been amended to specify

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			separately a group of people with moderate to severe disease.
	Roche Products	Within the DMARD-IR population, a subgroup of patients are expected to be on monotherapy biologic treatment (approximately one third, Soliman et al BSRBR 2011) which may be due to an intolerance or contraindication to methotrexate Biologic monotherapy treatments in this subgroup have yet to be reviewed as part of the NICE MTA process, although in the technology appraisal of tocilizumab (247) the Institute noted a lack of evidence in this sub-population. We are now in a position to provide head-to-head clinical trial evidence from the monotherapy setting, in the form of a randomised trial comparing tocilizumab and adalimumab monotherapies. We have also carried out a network meta analysis based on all available trials in the monotherapy setting, which allows the indirect comparison of tocilizumab, adalimumab, etanercept and certolizumab pegol, all of which have marketing authorisation to be given as monotherapy. We have also prepared an economic model based on this indirect comparison which enables comparison of alternative biologic monotherapy strategies, in a similar way to our economic model of biologic + methotrexate combination therapies. We would recommend that the Scope be altered to allow the consideration of the first head to head study of biologic RA treatments, as this may allow the revised TA130 to make an evidence-based recommendation around biologic monotherapy.	Comment noted. The appraisal will consider the products within their licensed indications including combination and mono-therapy as indicated.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	ScHARR-TAG	The scope explicitly says that "NICE has also issued guidance (TA195,	Comment noted. The

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		TA225 and TA 247) on the treatment of rheumatoid arthritis after the failure of a TNF inhibitor but this will not be addressed in this appraisal." This implies that sequencing will not be addressed within this appraisal, given that the five drugs are all classed as TNF inhibitors. I am presuming that the phrase did not respond adequately to conventional DMARDs includes those who responded adequately but suffered adverse events, and those who initially responded adequately but became resistant across time.	appraisal will consider where in the treatment sequence the first biologic should be considered for patients with moderate to severe and severe RA. It is expected that the economic analyses will be considered in the context of current clinical management which includes a sequence of treatments over the lifetime of the patient. This has been clarified in the scope.
	The Royal College of Nursing	.We would like to see include the use of biologics early in the pathway of patients' presenting with active disease & poor prognostic factors. In this group of patient early intervention could be potentially cost effective & this group could be examined separately.	Comment noted. The population has been amended to include patients with moderate to severe RA. Attendees at the scoping workshop noted that prognostic factors of worse outcomes had been identified. However, they considered that evidence would be in small patient numbers when also combined with consideration of moderate and severe disease

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Comparators	Abbott	Given that combination DMARD therapy is the recommended first line treatment in CG79, it would be helpful to clarify what should be modelled as second line treatment and further lines of therapy, e.g. addition of another DMARD to the failed combination or switch to an alternative DMARD therapy? It should be noted that only those drugs with a licence for treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate should be included as comparators for this population.	Comment noted. At the scoping workshop it was clarified that conventional DMARD therapy may include two DMARDs started concurrently, or it may include a step-up strategy. Submissions to NICE are expected to reflect current clinical practice taking into account existing clinical guidelines. Technologies will be appraised within their licensed indications. For the population of people biologic comparators are limited to those products also identified as interventions in the scope.
	AstraZeneca UK Ltd	We would like to understand the role of combination DMARDs in the treatment of rheumatoid arthritis in the UK and what the evidence base is to support the use of combination DMARDs. Our understanding from interactions with treating NHS clinicians is that combination DMARDs are rarely used compared to monotherapy.	Comment noted. Combination DMARD therapy is recommended for treatment naive rheumatoid arthritis as per NICE clinical guideline 79. Submissions to NICE are expected to reflect current clinical practice taking into account

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			existing clinical guidelines.
	Healthcare Improvement Scotland	There are head to head RCTs comparing abatacept and adalimumab, and tocilizumab and adalimumab. The relative cost effectiveness of both tocilizumab and abatacept should be considered - in fact the scope of the appraisal should be widened to assess the role of biologic therapy (not just TNFi therapy) The use of MTX/leflunomide combination is not an appropriate comparator as this combination is cautioned against. MTX/sulfasalazine/hydroxychloroquine is a more appropriate comparator	Comment noted. The appraisal has been expanded to include tocilizumab and abatacept. The scope does not specify particular combinations of conventional DMARDs. It is expected that submissions to NICE should reflect current clinical practice.
	MSD Ltd	For rheumatoid arthritis not previously treated with DMARDS, golimumab should be included, alongside infliximab, adalimumab and etanercept. As stated in the 'technologies' section, Golimumab (Simponi®) , in combination with methotrexate (MTX), is indicated for: • the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate. • the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX. Simponi, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.	Comment noted. The appraisal has been extended to include golimumab for people whose arthritis has not been previously treated with methotrexate.
	National Rheumatoid	Yes these are standard treatments currently used in the NHS which the technology should be compared to.	Comment noted. No action required.

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	Arthritis Society	NRAS believes that for patients who have failed conventional DMARDs, and then a subsequent first TNF inhibitor, the best alternative treatment at this point in the pathway would be to give them another biologic not a return to alternative conventional DMARDs.	
	Pfizer Ltd	We believe the comparators are correct with respect to the current interventions proposed in the draft scope.	Comment noted. No action required.
	Primary Care Rheumatology Society	Yes. We feel that best alternative care would be combination therapy with methotrexate plus at least 2 other DMARDs, such as O'Dell, FinRACo or COBRA studies.	Comment noted. No action required.
	Roche Products	This seems appropriate.	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	ScHARR-TAG	[redacted] Abatacept [redacted] should also fall within the appraisal.	Comment noted. Abatacept has been added to the appraisal as an intervention and comparator.
	UCB Pharma Ltd	It is not clear whether in the patient population not previously treated with DMARDs if one of the comparator arms will be stacked multiple DMARDs - i.e. two DMARDs (MTX plus another) given together. In clinical practice the alternative to a TNF in a new active patient would be the use of two concurrent DMARDs to eliminate this response before moving to consideration of a TNF inhibitor	Comment noted. At the scoping workshop it was clarified that conventional DMARD therapy may include two DMARDs started concurrently, or it may include a step-up strategy. Submissions to NICE are expected to

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			reflect current clinical practice taking into account existing clinical guidelines.

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Outcomes	Abbott	Improvements in work productivity for those of working age who are active in the labour force or improvements in ability to carry out normal daily activities for those not active in the labour force are useful outcome measures that should be added. These have been assessed for adalimumab through a variety of instruments such as the Work Productivity and Activity Impairment (WPAI) and Work Instability Scale (WIS).	Comment noted. The appraisal will be completed in accordance with the published methods guide. Productivity is not included in NICE technology appraisals
	AstraZeneca UK Ltd	We would like to see inclusion of work productivity as an outcome since this is very rarely captured by the ICER.	Comment noted. The appraisal will be completed in accordance with the published methods guide. Productivity is not included in NICE technology appraisals
	Healthcare Improvement Scotland	Yes from the perspective of the NHS but not from a societal perspective	Comment noted. The appraisal will be completed in accordance with the published methods guide. This includes NHS and PSS costs as well as HRQOL impacts to patients and to their caregivers.
	Pfizer Ltd	We agree with the current outcomes included in the draft scope. However, we suggest that the disease activity as an outcome should be split into primary loss of efficacy and secondary loss of efficacy. As RA is a chronic condition, duration of response and factors such as immunogenicity are likely to be important considerations for long term patient outcomes.	Comment noted. Disease activity is included as an outcome in the scope. Further specification of disease activity in any submission to NICE would be appropriate within

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			the current scope.
	Primary Care Rheumatology Society	Yes	Comment noted. No action required.
	Roche Products	Remission (DAS28<2.6) and low disease activity (DAS28: 2.6-3.2) are important outcomes in RA and should be included within the scope. The BSR 2009 clinical guidelines supports this outcome by noting that 'the aim of therapy is to minimize disease activity'.	Comment noted. The scope is intended to provide guidance on outcomes, but not to specify individual scales or other instruments. Disease activity is included as an outcome in the scope.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	ScHARR-TAG	As far as I am aware	Comment noted. No action required.
	UCB Pharma Ltd	Yes, however there is more detail needed. In the disease activity score we need to understand if this is ACR response, and if so whether it is a "blended" response rate covering ACR 20,50 and 70. There is a CRP response element to tocilizumab which is independent of physical function and disease activity which could confound effectiveness.	Comment noted. The scope is intended to provide guidance on outcomes, but not to specify individual scales or other instruments. Further specification of disease activity in any submission to NICE would be appropriate within the current scope
Economic	Abbott	It would be useful if clarification could be given regarding what resource use items are covered in the Personal Social Services perspective and whether any	Comment noted. NICE is not prescriptive in specifying in the

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analysis		additional costs of care for RA patients with high levels of functional impairment beyond those included in the NHS perspective would be included under this perspective?	methods guide costs covered under PSS. Further guidance may be found in the document Unit Costs of Health and Social care published by the PSSRU.
	AstraZeneca UK Ltd	No further comments	Comment noted. No action required.
	Healthcare Improvement Scotland	Fine	Comment noted. No action required.
	Primary Care Rheumatology Society	There is 11 year evience from the FinRACo and COBRA studies, so we feel that a time horizon of at least 10 years should be used for estimating clinical and cost effectiveness.	Comment noted. The time horizon in a model should be long enough to capture the costs and benefits of a disease. For a chronic disease such as RA where the treatments potentially modify the disease process, it would be expected that a life time horizon would be appropriate.
	Roche Products	Appropriate	Comment noted. No action required.
	Royal College of Pathologists	appropriate	Comment noted. No action required.
	ScHARR-TAG	-	Comment noted. No action required.

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Equality	Abbott	No further comments.	Comment noted. No action required.
	AstraZeneca UK Ltd	No further comments	Comment noted. No action required.
	Primary Care Rheumatology Society	We note that the UK is ranked 10th out of 15th countries in the usage of biological agents in rheumatoid arthritis, with UK usage only 73% of the international average (Extent and causes of international variations in drug usage:A report for the Secretary of State for Health by Professor Sir Mike Richards, July 2010). As rheumatoid arthitis is a major cause of disability, we feel that if more effective treatment can reduce disability it would help to promote equality and reduce discrimination against disability.	Comment noted. NICE is committed to ensuring equity of access to treatment for all groups with protected characteristics.
	Roche Products	n/a	Comment noted. No action required.
	Royal College of Pathologists	no concerns	Comment noted. No action required.
	ScHARR-TAG	-	Comment noted. No action required.
Other considerations	National Rheumatoid Arthritis Society	NRAS recommends the issue of access to biologic therapies is considered within the MTA process. A patient must record a disease activity score (DAS-28) of 5.1 or above to be eligible for TNF therapy, which is much higher than a number of other European countries and is having a an adverse impact on the clinical outcomes of a significant number of RA patients. According to "The extent and causes of international variations in drug usage: a report for the Secretary of State for Health, by Professr Sir Mike Richards	Comment noted. The population has been amended to include patients with moderate to severe RA.

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		CBE" (Department of Health, 2010), the UK ranked 10th out of 14 countries in terms of level of usage, despite joint analysis by the European Federation of Pharmaceutical Industry Associations, University of Lund and i3 Innovus showing that the price of biologics in the UK is amongst the lowest in Europe. Furthermore, according to evidence presented in the joint report, a DAS-28 score of between 3.2 and 5.1 is not benign as people with this scoring also suffer joint damage. The BSR and BHPR has also published "BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies" (2010), which also states that "biological therapies are recommended as options for the treatment of adults who have ...active RA as measured by DAS-28 >3.2 with at least three or more tender and three or more swollen joints". The LSE Policy Analysis Centre report on access to biologics in 12 countries, called "European Guideline Variations and Access to Innovative Therapies for Rheumatoid Arthritis" (2012) also states that in England "access to modern, biologic therapies is heavily restricted until a patient's burden of disease has become severe. Compared to other European countries this seems to be too little, too late." The eligibility criteria should therefore be lowered to enable more people with RA to access TNF inhibitors at a much earlier stage and the long-term economic benefits of this have been clearly outlined in the National Audit Office report of 2009.	
	Pfizer Ltd	If moderate to severe RA is considered as a separate population within the appraisal, then we would suggest, if evidence allows, that the appraisal looks at people with moderate rheumatoid arthritis with poor prognostic indicators at baseline.	Comment noted. The population has been amended to include patients with moderate to severe RA.
	Primary Care Rheumatology Society	We would like to see consideration being given to costs of social care, and loss of earnings due to sickness absence, both short and long term.	Comment noted. Social care costs may be included in the NICE reference case analysis

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			where these are personal social services costs. Productivity is not included in NICE technology appraisals.
	Roche Products	We agree that a review of the evidence on joint replacement and hospital admissions should be considered if the evidence allows. Further to this, a complete review of the costs associated with RA management would be appropriate, particulary any correlation that exists between disease severity and the resource burden on the NHS.	Comment noted. No action required. People providing submissions to NICE may include a review of the costs associated with RA management where these are considered relevant.
	Royal College of Pathologists	none	Comment noted. No action required.
	ScHARR-TAG	-	Comment noted. No action required.
	The Royal College of Nursing	.We would like to see NICE include in the treatment pathway, patient's with active Rheumatoid Arthritis (as defined by a DAS score of greater than 3.2 as per recent BSR guidelines (March 2010). Current NICE guidance restricts biologic use to patient with severe disease activity (DAS over 5.1) We think it is appropriate to review TA247 " Tocilizumab for the treatment of Rheumatoid arthrits" ….especially in patients unable to take Methotrexate, where there is new evidence relating to the efficacy/ superiority of Tocilizumab in this group of patients.	Comment noted. The population has been amended to include patients with moderate to severe RA. The scope of the appraisal has been extended to include a partial review of TA 247.
	UCB Pharma Ltd	We believe that since the initial review (TA130) the issue of work productivity and economic impact has become more significant. The NAO report and the review by the public accounts committee have highlighted the important of	Comment noted. The appraisal will be conducted in accordance with published

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		return to work and early intervention. The review should also focus on these benefits	NICE methods. Productivity is not included in NICE technology appraisals.
Questions for consultation	Abbott	Given the limited effective treatment options for patients with moderately active disease of DAS28 3.2 to 5.1 who have failed combination DMARD therapy Abbott considers that anti-TNF therapy for these patients would represent a step-change in the management of the condition. There is evidence that mapping algorithms from the HAQ to QALYs to assess Health-Related Quality of Life suffer from lack of accuracy as the impact on pain and mood is not fully captured by the mapping algorithm (Wolfe F, Michaud K and Wallenstein F, J Rheumatol 2010;37;1615-1625). Further Harrison and colleagues have presented evidence that the accuracy of mapping algorithms in inflammatory arthritis can vary across patient populations (Harrison et al. Health Qual Life Outcomes. 2010 Feb 11;8:21). As the impact of pain and fatigue is expected to be higher for more active disease, the use of mapping algorithms that do not take into account mood, pain and fatigue would result in an underestimation of utility scores, and of the benefit brought about by anti-TNF therapy in improving the patient experience on those dimensions. These additional benefits should be considered when evaluating the cost per QALY of anti-TNF therapy vs conventional DMARDs.	Comment noted. The population has been amended to include patients with moderate to severe RA. Consultees preparing submissions to NICE should include where benefits may not be captured in the QALY. The Committee may take into consideration benefits that are not adequately captured by QALY calculations.
	Healthcare Improvement Scotland	1. Yes, tocilizumab should be included 2. MTX naïve patients with adverse prognostic features should be considered as a sub-group 3. Yes, abatacept should be included 4. Evidence from RCTs is unlikely to capture reduction in mortality, reduction in CV end points which should be estimated using data from the BSR Biologics Register	Comment noted. The scope of the appraisal has been extended to include TA 234 and a part review of TA 247. Data from other study designs may be included in a submission to NICE where these provide information on

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			outcomes not fully captured in clinical trials.
	MSD Ltd	The alleviation of burden on carers of patients with RA is a potential significant and substantial health-related benefit which is unlikely to be included in the QALY calculation. In addition, improvements in productivity of care givers should also be considered.	Comment noted. The HRQOL impact to people providing care for people with RA may be included in the submission and economic analysis.
	National Rheumatoid Arthritis Society	NRAS believes it is not possible to accurately undertake an economic analysis of these treatments without also considering the associated impact on economic activity and productivity for the UK economy. RA impacts heavily on people of work age (it is most common after 40, and three-quarters of people with RA are first diagnosed when of working age) and it is a major cause of sickness absence and worklessness. The NRAS "I Want to Work" survey (2007) found that amost 30% of the people with RA surveyed gave up work as a result of their condition - with over 24 percent doing so within one year of diagnosis and well over half (59 per cent) doing so within six years. However, no comprehensive assessment has been completed so far to analyse the number and proportion of people able to make a return to work, or stay in work, as a result of being prescibed TNF inhibitors - and the resultant costs and benefits accruing to the Exchequer. NRAS would like to see much greater consideration of these issues during the course of the MTA process.	Comment noted. Comment noted. The appraisal will be conducted in accordance with published NICE methods. Productivity is not included in NICE technology appraisals.
	Pfizer Ltd	Etanercept is a human TNF receptor fusion protein with a distinct immunogenic profile. There is evidence to support its sustained efficacy and tolerability over more than 10 years in clinical practice. Since the last NICE appraisal, further trial evidence of TNF-alpha inhibitors in a	Comment noted. The population has been amended to include patients with moderate to severe disease.

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		moderate RA population has been published, providing a further reason for the inclusion of moderate to severe RA as a separate population within the scope.	The time horizon in a model should be long enough to capture the costs and benefits of a disease. For a chronic disease such as RA where the treatments potentially modify the disease process, it would be expected that a life time horizon would be appropriate. .
	Primary Care Rheumatology Society	We feel that consideration needs to be given to widening access to these drugs so that people with less severe, and/or earlier, disease can be treated as we feel that this would make a significant and substantial impact on the health of this population. This has the potential to be a "step-change" in the treatment of rheumatoid arthritis, and holds out the potential of long-lasting health benefits even after treatment is withdrawn (Quinn MA, et al Arthritis & Rheumatism, 2005, 52:1, p27-35).	Comment noted. The population has been amended to include patients with moderate to severe RA.
	Roche Products	As discussed above, we recommend that the Scope should separately address the subgroup of patients in whom treatment with methotrexate would not be appropriate due to intolerance, contraindication or other concerns. With a new head to head trial of two biologic monotherapies (tocilizumab and adalimumab) available, we believe there is a good case to review existing recommendations around biologic monotherapy. In respect of the question of whether TA 247 (tocilizumab) should be included in the currently-proposed MTA review, we are not aware of any new evidence which would materially alter the recommendations in TA 247, save for the monotherapy data, analyses and economic model which we are now in a position to provide to the Institute. Therefore it is our view that TA 247 does not need a full update, but that TA 130 and TA 247 should be updated to take into	Comment noted. The appraisal will consider the products within their licensed indications including combination and mono-therapy as indicated. The scope of the appraisal has been extended to include a partial review of TA 247. The final scope will not be changed after the invitation to participate has been issued, so that this MTA review guidance is produced in

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		account the Institute's consideration of the new monotherapy evidence. We would also request that the Institute provide clarification on whether the wording in TA 247 guidance, which refers extensively to recommendations within TA 130, is expected to require updating in the event of any substantial changes to TA 130. We feel that the place of TA 130 in relation to the treatment pathway is appropriately defined. However, we recognise the challenges which may be associated with evaluating evidence from earlier in the treatment pathway. We are not yet certain as to whether we will be in a position to provide data about tocilizumab's use in settings earlier than DMARD-IR, nor whether it will be awarded a marketing authorisation in earlier settings, within the proposed timeframes of this MTA. However, should any evidence or licensing timelines become available to us in time, we will endeavour to work with the Assessment Group to enable data about earlier indication(s) to be incorporated.	a timely fashion.
	Royal College of Pathologists	yes	Comment noted. No action required.
	ScHARR-TAG	a) No b) No	Comment noted. No action required.
	The Royal College of Nursing	The use of modified DAd criteria for eligibility of first biologic & continuation of effective biologic therapy for patirnts with RA as detailed by the BSR in its guidance published in March 2010	Comment noted. The population in the scope has been amended to specify separately a group of people with moderate to severe RA. The scope is intended to provide guidance on outcomes, but not to specify individual scales or other

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			instruments.
	UCB Pharma Ltd	The earier use of TNF blockers will potentially allow earlier remission and the avoidance of disability through lower levels of joint damage at a much earlier stage in the disease course. The current practice of allowing patients to progress in their condition to a higher degree of severity is simply allowing avoidable harm to occur before effective treatment.	Comment noted. The appraisal includes consideration of the earlier use of TNF inhibitors where they are licensed for use.
Other considerations (continued)	Abbott	Is it appropriate to include a review of the guidance in TA247, 'tocilizumab for the treatment of rheumatoid arthritis' that considers the use of tocilizumab only after the failure of conventional DMARDs? Abbott considers that it would not be appropriate to include drugs outside the anti-TNF class in this MTA review as these drugs have a different mechanism of action and have been licensed for shorter time periods than the anti-TNF class, therefore the risk benefit profile may vary. This can be seen in the fact that only anti-TNF drugs are licensed as treatment options for methotrexate naïve patients. Inclusion of additional drug classes will increase the complexity of this MTA and potentially increase the time to final guidance if additional analyses are required. Given that the previous guidance has not been updated since 2007 and there is increasing evidence that anti-TNF therapy would represent a step change in management of patients with moderate disease activity, Abbott considers the need to ensure timely guidance may be helped by restricting this MTA review only to anti-TNF drugs. Is it appropriate to include an appraisal of the terminated guidance TA225 'golimumab for the treatment of methotrexate naive rheumatoid arthritis'? Yes, it would be appropriate to include golimumab as a treatment option for methotrexate naïve patients. Is it appropriate to include a review of the guidance for abatacept in TA234, 'abatacept for the treatment of rheumatoid arthritis after the failure of	Comment noted. At the scoping workshop it was agreed that it was appropriate to include other biologic therapies. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224).

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		conventional disease-modifying anti-rheumatic drugs'? No, as outlined above Abbott considers that it would be preferable to restrict this MTA review to anti-TNF drugs only	
	AstraZeneca UK Ltd	We would like to query the relevance of a methotrexate-naive population in the terminated golimumab appraisal and believe it should not be included in the MTA. We would welcome the inclusion of the abatacept appraisal into the MTA and believe the inclusion will assist the NHS in developing a treatment pathway for rheumatoid arthritis that dleivers value for money. Rheumatoid arthritis is a heterogenous disease and we would like the MTA to also inform clinicians whether it is best to treat rheumatoid arthritis patients with sequential use of anti-TNFs or to treat with an agent with a new mode of action after having progressed. This MTA has 5 technologies which have an anti-TNF mode of action and we would welcome the inclusion of other biological agents to ensure clinicians can make an informed decision on the choice of technologies to treat rheumatoid arthritis	Comment noted. At the scoping workshop it was agreed that it was appropriate to include golimumab for RA not previously treated with methotrexate and other biologic therapies. The scope of the appraisal has been extended to include a review of TA 234. The appraisal will also consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224.
	BMS	It is appropriate to include tocilizumab, golimumab and abatacept in the scope of this appraisal.	Comment noted. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224).
	MSD Ltd	MSD believes that an appraisal of the terminated guidance TA225 'golimumab	Comment noted. The scope of

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		for the treatment of methotrexate naïve RA' should be included in this MTA. The British Society of Rheumatology Guidelines for Eligibility for First Biological Therapy currently reflect NICE recommendations, however the BSR hopes to see a broadening in the eligibility for RA patients in the near future. (ref. Deighton C et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. 2010 doi:10.1093/rheumatology/keq006b Available at: www.rheumatology.org.uk Accessed 15th August 2012). Current NICE guidance states that patients must have a DAS-28 > 5.1 on two occasions one month apart and have failure of two conventional DMARDs to be eligible for biologic therapy. However, the BSR recommend therapy for patients with a DAS-28 > 3.2. This would be in line with other European countries including Sweden and Holland. Existing NICE guidance, does not support the use of any TNF inhibitor for patients with severe, active and progressive rheumatoid arthritis not previously treated with methotrexate. As such, current clinical practice is in line with NICE guidance and use of biologics for the treatment of methotrexate naïve RA is not standard practice. MSD believes that expanding the remit of this MTA to include treatment of patients with moderate disease (DAS-28 > 3.2) and golimumab for the treatment of methotrexate naïve RA will support the goal of the BSR and broaden the eligible population and choice for RA patients.	the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224). The population has been amended to include patients with moderate to severe RA.
	National Rheumatoid Arthritis Society	In the interests of unifying and simplifying the number of technology appraisals for rheumatoid arthritis, NRAS would like to see the scope include a review of the following guidance: - TA247 Tocilizumab for the treatment of rheumatoid arthritis after the failure of conventional DMARDS	Comment noted. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people

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		- TA225 golimumab for the treatment of methotrexate naive rheumatoid arthritis patients - TA234 abatacept for the treatment of rheumatoid arthritis after the failure of conventional DMARDs.	with RA not previously treated with methotrexate (terminated TA 224).
	Pfizer Ltd	Are the interventions in the apprasial appropriately define? Should the review include other technologies? The appraisal is appropriately defined if the objective of the review is to look at current TNF-alpha inhibitors. If the objective of the current review is to appraise biologic therapies then tocilizumab should be included as an intervention within the scope. Golimumab should be included in the review as it is an applicable intervention given its license for MTX naïve RA patients and it is a TNF-alpha inhibitor. We would suggest that abatacept should only be included in the appraisal if there is new evidence that improves the clinical and cost effectiveness of abatacept, which is likely to change current NICE recommendations. Is the place in the treatment pathway appropriately defined? Should the review include additional places in the treatment pathway? The review should also include a review of TNF-alpha inhibitor monotherapy, which is not currently explicitly mentioned within the scope, but occurs in UK clinical practice and is currently recommended by NICE. Are the subgroups suggested in other considerations appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? We would suggest that if evidence allows that the appraisal looks at people with moderate rheumatoid arthritis with poor prognostic indicators at baseline.	Comment noted. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224). The products will each be considered within their licensed indications including combination and monotherapy as indicated. Comment noted. The population in the scope has been amended to specify separately a group of people with moderate to severe RA.

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	Royal College of Pathologists	Are the interventions in the appraisal appropriately defined? Should the review include any other technologies? YES • Is it appropriate to include a review of the guidance in TA247, 'tocilizumab for the treatment of rheumatoid arthritis' that considers the use of tocilizumab only after the failure of conventional DMARDs? YES • Is it appropriate to include an appraisal of the terminated guidance TA225 'golimumab for the treatment of methotrexate naive rheumatoid arthritis'? YES • Is it appropriate to include a review of the guidance for abatacept in TA234, 'abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs'? YES Is the place in the treatment pathway appropriately defined? YES Should the review include additional places in the treatment pathway? NO Have the most appropriate comparators for adalimumab, etanercept, infliximab, certolizumab pegol and golimumab for the treatment of rheumatoid arthritis been included in the scope? YES Are the comparators listed routinely used in clinical practice? YES Are the subgroups suggested in 'other considerations appropriate? YES Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? NO	Comment noted. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224).
	ScHARR-TAG	Whilst acknowledging that it would make the appraisal more resource intensive, reappraising the guidance for tocilizumab, golimumab and abatacept could be beneficial and the constraints of an STA would not apply to an MTA. However, should NICE wish to formally consider sequencing of the TNFs then it should be noted that the resource costs of the addition of these drugs will be	Comment noted. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will

Section	Consultees	Comments	Action
		significantly higher.	consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224). The appraisal will consider where in the treatment sequence the first biologic should be considered for patients with moderate to severe and severe RA. It is expected that the economic analyses will be considered in the context of current clinical management which includes a sequence of treatments over the lifetime of the patient. This has been clarified in the scope.
	UCB Pharma Ltd	Tocilizumab should be included as a comparator. Golimumab for the treatment of MTX naïve patients should be considered. A review of abatacept in DMARD IR patients should be included. As these therapies are likely comparators it is logical to include them in the appraisal. If they are not comparators then a straight comparison between TNF inhibitors should be carried out	Comment noted. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234. The appraisal will consider golimumab for people with RA not previously treated with methotrexate (terminated TA 224).
Any additional comments on	ScHARR-TAG	The current wording suggests that this appraisal intends purely to be focussed on at what level each intervention is cost-effective following use of DMARDs or	Comment noted. The appraisal will consider where in the

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the draft scope		not dependent of contraindications. Is the intention to omit all downstream costs beyond this point or to assemble a generic pathway that all patients would follow after failure on the initial intervention. In previous NICE appraisals the use of first line treatments (eg in PAH) necessitated the modelling of a full sequence. The current scope does allow the analysis of etanercept against cDMARDs in first line treatment. If etanercept was shown to be most cost-effective then this may leave a position where following etarnacept patients would need to be given cDMARDs as the guidance in TA195 indicates a second TNF can only be provided following cDMARDs and the first TNF.	treatment sequence the first biologic should be considered for patients with moderate to severe and severe RA. It is expected that the economic analyses will be considered in the context of current clinical management which includes a sequence of treatments over the lifetime of the patient. This has been clarified in the scope.
	UCB Pharma Ltd	The position in the treatment pathway is unclear; are the committee considering the use of a TNF inhibitor in DMARD treatment naïve patients as one pathway and DMARD IR patients as a second pathway? Guidance on the optimal approach to DMARD therapy prior to TNF inhibitor use would be a helpful aspect to the guiance. Finally is the committee looking to evaluate a sequence with rituximab as a follow up therapy?	Comment noted. The appraisal will consider where in the treatment sequence the first biologic should be considered for patients with moderate to severe and severe RA. It is expected that the economic analyses will be considered in the context of current clinical management which includes a sequence of treatments over the lifetime of the patient. This has been clarified in the scope. The guidance for rituximab and the use of biologics after the failure of a TNF inhibitor are not included in this review.

The British Society for Rheumatology submitted comments on the draft scope that were identified after the invitation to participate in this appraisal was sent out. Their comments are included below, alongside a response.

Comment: the draft scope

Section	Consultees	Comments	Response
Background information	BSR	We consider it to be accurate although the use of corticosteroids is underemphasised.	Comment noted. The background section of the scope provides a brief overview of the condition. Further information about the condition and its management should be included in any submissions to NICE.
The technology/ intervention	BSR	Yes	Comment noted. No changes requested.
Population	BSR	The eligibility for treatment is not defined. We would like NICE to include the eligibility criteria for initiation of treatment as part of the scope. We consider that it is currently unnecessarily strict. We would like the British Society for Rheumatology Guidelines on eligibility for first biologic to be considered in discussions (http://www.rheumatology.org.uk/includes/documents/ cm_docs/2010/r/2_ra_guidelines_on_eligibility_criteria_ for_the_first_biological_therapy.pdf.)	Comment noted. The appraisal will consider the criteria for the initiation of treatment in terms of identifying the most appropriate use of NHS resources. It was agreed at the scoping workshop that the population in the scope should specify separately a group of people with moderate to severe active RA and severe active RA.
Comparators	BSR	We consider the comparators to be appropriate	Comment noted. No changes requested.

Section	Consultees	Comments	Response
Outcomes	BSR	We are satisfied with the list of outcomes. However, we are concerned that there was an overemphasis of the HAQ disability score in previous assessments and this underestimated the response of disabled patients as the reduction in HAQ score in patients with permanent disabilty from joint damage may be small (ie their level of disability may be irreversible) but the improvement in joint pain and stiffness from treatment may still be clinically significant. We consider that a broader evaluation of response in severely disabled patients needs to be emphasised in the scope.	Comment noted. The outcomes section of the scope specifies the types of outcomes that are relevant to the appraisal. Consultees preparing submissions to NICE should include information about the advantages and disadvantages of different outcome measures, including where their use may result in benefits not being captured in the QALY. The Committee may take into consideration benefits that are not adequately captured by QALY calculations.
Economic analysis	BSR	We consider the appropriate time horizon should be at least 12 months	Comment noted. The time horizon in a model should be long enough to capture the costs and benefits of a disease. For a chronic disease such as RA where the treatments potentially modify the disease process, it would be expected that a life time horizon would be appropriate.
Equality and Diversity	BSR	We are concerned that disabled patients should have access to appropriate treatment.	Comment noted. NICE is committed to ensuring equity of access to treatment for all groups with protected characteristics. Information about possible equalities issues should be included in submissions to NICE. The appraisal Committee will consider any potential equality issues throughout the appraisal process.

Section	Consultees	Comments	Response
Other considerations	BSR	We consider that both tocilizumab and abatacept should be included in the scope	Comment noted. The appraisal will include both tocilizumab and abatacept. The scope of the appraisal has been extended to include a partial review of TA 247, and a review of TA 234.
Questions for consultation	BSR	The technologies may offer major health benefits and may be considered as a step change in the management of patients. As described above there can be a difficulty in measuring the response in very disabled patients if there is an overemphasis on the HAQ scores. We consider that the assessments of clinical benefit should not be dictated only by an improvement in disabilty.	Comment noted. The outcomes section of the scope specifies the types of outcomes that are relevant to the appraisal. Consultees preparing submissions to NICE should include information about the advantage and disadvantages of different outcome measures, including where their use may result in benefits not being captured in the QALY. The Committee may take into consideration benefits that are not adequately captured by QALY calculations.
		We do not have concerns regarding golilimumab in MTX naïve patients.	Comment noted. Following the scoping workshop the scope was expanded to include a review of the terminated guidance for the use of golimumab in RA not previously treated with methotrexate.
		Unfortunately there are no subgroups that have been identified that predict clinical response. The presence of autoantibodies has not been a useful clinoical indicator of response (except with rituximab).	Comment noted. It was agreed at the scoping workshop that there were no subgroups that should be specified in the scope.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Novartis Pharmaceuticals

British Health Professionals in Rheumatology (BHPR)

Department of Health

Medicines and Healthcare products Regulatory Agency (MHRA)

Royal College of Physicians endorses BSR position